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THE "TYPHOID-CARRIER" STATE IN RABBITS AS A METHOD OF DETERMINING THE COMPARATIVE IMMUNIZING VALUE OF PREPARATIONS OF THE TYPHOID BACILLUS

*STUDIES IN TYPHOID IMMUNIZATION. I**

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INTRODUCTORY

Prophylactic immunization against typhoid fever offers sufficient security against subsequent infection to render its general application advocable. Such application is not only becoming wide-spread and mandatory in segregated, controllable bodies like armies, but has proved very advantageous in communities in general. In surveying the already extensive statistical literature, one becomes convinced of the relative protection against typhoid fever that is enjoyed by those who have been immunized with preparations of the typhoid bacillus; one is likewise convinced that the results obtained and the methods of immunization followed leave much to be desired.

Why should the results of immunization against typhoid infection be less perfect than those obtained in small-pox and rabies? Why should artificial immunization with the typhoid bacillus offer so much less perfect protection than recovery from typhoid fever? In respect to the method employed we may well question why 500,000,000 killed typhoid bacilli is the recommended dose, and why the interval at which this dose should be repeated is arbitrarily set at seven or ten days. The fact is that we possess only too little information of an exact sort about methods of prophylactic immunizing with bacteria in general. In the case of antityphoid immunization, empiricism rather than experimentation, has largely determined the method employed. The results attained are so good that they should be better, and it would seem that the time has arrived to return to animal experimentation in order to save time in determining the ultimately best method of protecting man.

The best evidence that the most satisfactory method has yet to be determined lies in the fact that a number of methods are still being

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advocated. Friedberger,[1] in his exhaustive article on antityphoid immunization, mentions no less than twelve well-recognized preparations of the typhoid bacillus which may be employed. Paladino Blandini[2] has actually endeavored to test the comparative immunizing value of seventeen different typhoid preparations. In addition to the actual preparation to be employed, we have to consider the dose used, the method of estimating the dose, the intervals between doses and the like.

The chief reason why animal experimentation has not done more to perfect the method of typhoid vaccination is the reasonable skepticism which obtains at transferring results attained in a vastly different and artificial infection in animals to a very characteristic human disease. There seems little or no resemblance between the more or less common type of peritonitis produced in the guinea-pig by the typhoid bacillus and actual typhoid fever. Until very recently it has been supposed that nothing resembling typhoid fever in man could be produced in animals. In 1911, Metchnikoff and Besredka[3] described a disease in chimpanzees which had been given food contaminated with the excreta from typhoid fever patients, which resembled in practically all details the human syndrome. They further attempted to utilize this experimental disease as a means of comparing the immunizing value of various typhoid preparations. Their results even in the limited aspect of the problem they attacked can hardly be regarded as conclusive in view of the necessarily small number of animals employed and the fact that their tentative results differ from what is known to be true in man. We shall consider their report more fully later, but here it may be noted simply that desirable as tests might be in the experimental disease most closely simulating typhoid fever in man, it would be impossible from the item of expense and supply alone to carry out any extended experiments on these animals.

PRODUCTION OF AN ARTIFICIAL TYPHOID-CARRIER STATE IN RABBITS

It has been known since the observations of Blackstein[4] and Welch[5] in 1891, that living typhoid bacilli injected into the circulation of rabbits can subsequently be recovered in pure culture therefrom, for considerable periods of time. Further work has served to explain the nature of this

1. Friedberger: Die Methoden der Schutzimpfung gegen Typhus, Kraus and Levaditi's Handbuch der Immunitätsforschung, 1908, i, 723.

2. Paladino, Blandini: Profilassi specifica del tifo addominale, Ann. d'ig. sper., xv, 1905, 295.

3. Metchnikoff and Besredka: Recherches sur la fièvre typhoïde experimentelle, Ann. de l'Inst. Pasteur, 1911, xxv, 193.

4. Blackstein: Intravenous Inoculation of Rabbits with Bacillus Coli Communis, and the Bacillus Typhi Abdominalis, Bull. Johns Hopkins Hosp., 1891, ii, 96.

5. Welch: Additional Note Concerning the Intravenous Inoculation of the Bacillus Typhi Abdominalis, Bull. Johns Hopkins Hosp., 1891, ii, p. 121.

"carrier" condition more fully. The injections must be intravenous to yield positive results,[6] and it is evident from the varying success of different observers that not all strains of the typhoid bacillus give equally good results. It is clear from the results of Morgan,[7] Koch,[8] Doerr,[9] and Johnston,[10] that the permanent reservoir of the organism is the gall-bladder, which is invaded within two hours after intravenous inoculation.[6] It may be that, under usual conditions, the circulation is only invaded periodically, which would explain why Johnston failed to get positive cultures from the blood with regularity before the period from the seventh to the tenth day, and also would indicate the reason why Doerr failed to obtain positive blood-cultures after the fourth day. It is certain that failure to produce a carrier should not be judged from a single blood-culture. At all events, cultures from the gall-bladder are positive more constantly and for longer periods than cultures from the blood. Constant lesions of the gall-bladder have been described by Chirolanza in particular and will be further detailed in connection with our own protocols.

The persistence of the typhoid bacillus in the rabbit has been noted for varying lengths of time: in the blood for 58 days (Chirolanza); 109 days (Blackstein); 127 days (Johnston); and in the gall-bladder for even longer periods: 180 days (Uhlenhuth and Messerschmidt[11]); 75 days (Morgan); 120 days (Doerr). The organisms are apparently eliminated through the intestine in which they have been found by Doerr in the mucosa up to 120 days after inoculation. They were likewise repeatedly found in the feces by Morgan and by Johnston.

The actual pathogenicity for rabbits of strains of the typhoid bacillus capable of producing the carrier state in these animals does not appear to have received particular attention from previous observers. Morgan mentions, without further particulars, that two out of twelve of his animals died in twelve hours. Similar observations were made by Chirolanza. Johnston mentions the obtaining of positive cultures from bile and blood in nearly all fatal cases, but does not give the percentage of carrier rabbits that died. Another point of particular interest in view of our employment of the carrier state as a means of demonstrating the

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6. Chirolanza: Experimentelle Untersuchungen über die Beziehung der Typhusbacillen zu der Gallenblase und den Gallenwegen, Ztschr. f. Hyg. u. Infectionskrankh., 1909, lxii, 11.

7. Morgan: Attempts to Produce the Typhoid-Carrier State in the Rabbit, Jour. Hyg., 1911, xi, 202.

8. Koch. Typhusbacillen und Gallenblasen, Ztschr. f. Hyg., 1909, lxii, 1.

9. Doerr: Experimentelle Untersuchungen über das Fortwuchern von Typhusbacillen in der Gallenblase, Centralbl. f. Bakteriol., 1905, Orig. xxxix, 624.

10. Johnston: Experimental Typhoid-Carrier State in the Rabbit, Jour. Med. Research, 1912, xxvii, 177.

11. Uhlenhuth and Messerschmidt: Versuche Kaninchen zu Typhusbacillen-Trägern zu machen und sie therapeutisch zu beeinflussen, Deutsch. med. Wchnschr., 1912, xxxviii, 2393.

absence or presence of an active immunity is the uniform presence of agglutinins in positive rabbits (Morgan, Johnston, Doerr).

The typhoid-carrier state in rabbits has been used as a means of testing certain therapeutic measures. Conradi[12] has shown that daily doses of chloroform in oil or milk given by the rectum suffice to cure the carrier rabbits. Hailer and Rimpau[13] have obtained similar results with methyl iodid and iodoform. Johnston has been able to cure the bacteremia by two doses of 20,000,000 killed typhoid bacilli.

To meet our experimental needs, it was necessary that we should be able to produce a typhoid bacillemia with regularity, since the efficacy of a given method of vaccination could be judged only by the failure of properly protected animals to become carriers, whereas the normal controls should give positive results uniformly. The irregularity in the results of other observers was not very encouraging, and our own first results were even less so.

It seems to us that no wholly satisfactory method of obtaining an exact dosage of living bacteria has been devised. Perhaps the least objectionable method consists in employing a given portion of a suspension of a standard agar surface, particularly when the dose is of necessity large, as in the present case. In order to obtain comparable results in different experiments, we have used thick-walled culture-tubes of uniform size (inside diameter 18 mm.), containing 10 c.c. each of a 2 per cent. peptone agar, or in the majority of our experiments agar containing 10 per cent. defibrinated rabbit blood. These tubes are slanted at a fixed angle of about 6 degrees, so that the entire solidified surface is, within a small margin of error, uniform. Twenty-four-hour growths of such cultures suspended in salt solution have been used in amounts representing fractions of an original culture. By plating out these blood-cultures, we estimate that each one contains 1,400,000 million organisms. The blood-cultures are more abundant than corresponding agar-cultures.

The first five strains of *Bacillus typhosus* tested, which included three from the collection of the California State Board of Health Laboratory, Army and Navy Strain 5 obtained from the Cutter Laboratory, and one strain (65), obtained from Professor Zinsser, in an intravenous dose of the entire standard agar-culture previously referred to, failed to produce carriers, to kill, or seriously to affect rabbits which weighed from 1,500 to 2,000 gm. Two other cultures gave positive results, Culture 6 killing a small rabbit in twenty hours, and Strain 3, which had been isolated two weeks previously from a human blood-culture, produced a carrier that gave a positive culture ten days later. The reisolations from these two

12. Conradi: Ueber sterilisierende Wirkung des Chloroform im Tierkorper, Ztschr. f. Immunitätsforsch., 1910, vii, 158.

13. Hailer and Rimpau: Versuche über Abtotung von Typhusbacillen in Organismus, Arbeit. a.d.k. Gsndhtsamte, 1911, xxvi, 409.

animals were made on rabbit-blood agar. All of our subsequent experimental work has been carried on with cultures grown on this medium. To this procedure we attribute, at least in part, our present success in producing a bacteriemia regularly. Since our first success in producing a carrier with a whole standard agar-culture of Strain 3, we have failed with subsequent generations of the culture grown on agar to produce carriers, whereas the blood-agar cultures produce carriers regularly. Inasmuch as the growth on the blood-medium is more abundant, a little less than twice the amount of the agar growth by weight, we have used a whole agar-culture in comparing its infectiousness with half a blood-agar culture. Culture 6, which in a dose of a whole agar-culture killed the first rabbit in twenty hours, in the first blood generation from this animal (Culture 6a) failed to produce a bacteriemia in a dose of one-half of a culture, and the strain was abandoned for Culture 3a and subsequent generations, which gave positive results in this dosage.

A survey of our protocols in which groups of vaccinated rabbits were tested with normal controls, shows that one-half of a standard blood-culture of our Strain 3 of *B. typhosus* produces with almost perfect regularity characteristic pathogenic effects which do not occur in properly protected animals. Smaller doses, as one-quarter of a culture, produce less consistent results. Thus of seventeen control animals used in our latest experiments we find: 1. Three died in from two to twenty-four hours with symptoms of acute intoxication. 2. Thirteen gave one or more positive cultures of *B. typhosus* from the blood[14] at periods from the fifth to the twenty-eighth day, and of these animals five died between the fifth and twentieth day. Of the other eight, only one certainly recovered, as shown by negative cultures from bile and blood; through error, four animals were not observed over a sufficient period of time to know whether they would have died or recovered. 3. Only one animal gave apparently negative results. Cultures from the blood were negative on the sixth, eighth and twentieth day, and when the animal was killed by bleeding on the thirty-fifth day, cultures from the gall-bladder and blood were also negative. The animal, however, showed extreme loss of weight (2,440 to 1,710 gm. on the thirtieth day), and the blood-serum on the thirty-fifth day agglutinated the typhoid bacillus in a dilution of 1 to 2,000.

The carrier state in rabbits is not accompanied by any distinctive or continuous rise in temperature.

Chirolanza has given a full description of the lesions he found associated with the typhoid-carrier state in rabbits, and a few observations

14. The routine cultures are taken by allowing 10 drops of blood to drop from the carefully cleaned ear vein into bile bouillon. If contaminations are evident, which is rarely the case, the culture is plated out. (Culturally probable typhoid bacilli are tested with an agglutinating serum.)

have also been made by Morgan. The lesions affect the gall-bladder primarily and to a less extent the liver and bile ducts. According to Chirolanza, animals dying in the first few hours after inoculation show cloudy swelling, subcapsular hemorrhages and zonal necroses of the liver. The gall-bladder is not at first affected, but after a day or two the mucosa becomes necrotic. The later changes in this organ are more characteristic and consist in proliferation of the mucosa of the gall-bladder, more rarely a loss of mucosa and thickening of the fibromuscular coat; thickening of the bile-duct and gradual lymphoid infiltration and cirrhosis of the liver.

Although we do not pretend to offer any systematic study of the morbid anatomy of this condition, certain constant lesions are noted in our protocols.

In rabbits in which death is rapid, that is, within twenty-four hours, the gall-bladder shows no changes; the liver shows chronic passive congestion and usually central necrosis of the lobule. We have not studied the intermediate period in any detail, but beginning with the second week certain characteristic changes are to be noted. At necropsy the gall-bladder is uniformly distended and frequently is four or five times the usual size. The bile is usually cloudy or contains visible flocculi and at times a mass of inspissated bile salts is present that fills and distends the gall-bladder. In our experience complete destruction of the mucosa and reduction of the wall to a thickened fibromuscular coat is more frequent than the proliferation described by Chirolanza. We have been unable to convince ourselves of any constant changes in the liver beyond the early zonal necrosis, that is characteristic of bacterial infections in general.

It is of importance in justifying our use of the typhoid-carrier rabbit and in showing that conditions in these animals are analogous to the conditions in typhoid infection in man, to note that the lesions of the gall-bladder in typhoid cases in man are quite similar to those in the infected rabbits. J. Koch has compared these conditions very carefully, using his own and Chirolanza's material. He has further shown that the infection of the bile in man and in the rabbit is through the circulation and not from the intestine by way of the bile duct. The analogy of the lesions in man and in the rabbit is also emphasized by Uhlenhuth and Messerschmidt.[11]

We have further found marked injection of the cecum in two instances, and actual hemorrhage in one instance in carriers, similar to those produced regularly by the toxin of the typhoid bacillus.[15]

We find, then, that the intravenous injection of a uniform amount of a rabbit-blood agar-culture of our strain of *B. typhosus* produces an almost invariable and characteristic syndrome in normal rabbits (94 per

15. Arima: Ueber die Typhustoxine und ihre pathogene Wirkung, Centralbl. f. Bakteriol., Orig., 1912, lxiii, 424.

cent. positive). They either die with acute symptoms of intoxication within the first few hours and without characteristic lesions (18 per cent.) or become more or less chronic carriers (76 per cent.), yielding positive cultures from the blood for two or three weeks, within which time many of them die. Cultures from the gall-bladder of these animals are even more uniformly positive than the blood-cultures, and the bladder itself shows characteristic lesions in the distention and necrosis of the mucosa. The bile becomes inspissated in the majority of cases. Inadequately immunized animals give the same result.

We do not wish at this time to consider in detail the methods of comparative prophylactic immunization with the preparations of the typhoid bacillus that we have employed, but reserve it for a separate report, when our already considerable data have been further amplified. It may suffice to say that we have been comparing dead and living cultures of the organisms, sensitized (Besredka) and unsensitized cultures, and, finally, various fractions of dried and ground bacilli. It will suffice at this point to state that animals which have been fully immunized with, let us say, whole dried and ground preparations of *B. typhosus,* show no ill effects on injection of the standard amount of living blood-culture. The properly protected animals, following the test intravenous inoculation, show no considerable loss of weight, give uniformly negative cultures from twenty-four hours on, and when killed at considerable periods (from twenty-one to thirty-five days) subsequently, present uniformly negative findings at necropsy. In other words, this intravenous method of inoculation has given a nearly perfect method of comparing the relative immunizing property of various preparations of the typhoid bacillus. The small margin of error (6 per cent. in our series) incident to the failure of the exceptional normal animal to give positive results may be corrected by using a sufficient number of animals in testing each immunizing preparation.

It remains to discuss the extent to which we believe we are justified in regarding the carrier condition in rabbits as analogous to a typhoid infection in human beings. The work of recent years on typhoid fever in man has led to considerable readjustment of our ideas as to its pathogenesis. To quote Kolle and Hetsch,[16] we no longer regard typhoid fever as an intestinal disease, but primarily as a bacteriemia. This statement is based first on the fact that blood-cultures taken in the first week of the disease in an appropriate manner yield positive results in 100 per cent. of cases (Brion and Kayser).[17] The bile also gives positive cultures in

16. Kolle and Hetsch: Die experimentelle Bakteriologie und die Infektions-Krankheiten, Berlin, 1911, i, 250; 3d edit., Urban und Schwarzenberg.

17. Brion and Kayser: Neuere Klinisch-bakterologische Erfahrungen bei Typhus und Paratyphus, Deutsch. Arch. f. Klin. Med., 1906, lxxxv, 552.

practically all cases and at all stages of the disease (Forster and Kayser[18]). The occurrence of cases of typhoid fever without intestinal lesions is another reason for regarding these typical lesions as secondary rather than primary.[19] There is evidence, indeed, that the lesions in the ileum may be eliminative and secondary to the bacteriemia rather than a primary focus of the disease. The proliferation of lymphoid tissue in the intestine and elsewhere characteristic of the disease has been logically attributed to the typhoid toxins (Mallory) rather than to simple multiplication of the bacillus.

The mere fact, then, that the injection of living typhoid bacilli in rabbits does not lead to the characteristic swelling and necrosis of the agminated follicles of the intestine, as is usual in typhoid fever, is no reason for regarding the rabbit syndrome that we have described as essentially dissimilar from the condition in man. In both rabbit and man the typhoid bacillus remains for considerable periods in the circulating blood, and in both it promptly invades the bile by means of the circulation and not by the bile duct (J. Koch, Doerr, Chirolanza). It remains in both human and rabbit carriers in the gall-bladder even after it has disappeared from the circulation and in both cases it is subsequently eliminated through the intestinal mucosa. The characteristic result of gall-stone formation which may follow typhoid infection in man has also been produced in rabbits by Richardson[19] by giving calcium. It has been noted that the intestinal lesions may more properly be attributed to eliminated toxins of the typhoid bacillus, and it is interesting to note that similar lesions may be produced in rabbits by the use of typhoid toxins[15] instead of living cultures. We have obtained similar results with killed cultures of *B. typhosus* in sufficient doses. Arima produces by means of intravenous injection of his "endotoxin" of *B. typhosus,* bloody diarrhea, hyperemia, swelling and hemorrhage of the intestinal lymph-nodes.

We regard these facts as indicating the very close analogy of infections produced by the typhoid bacillus in man and in the rabbit. Apart from its intrinsic value as a clean-cut experimental method, the rabbit "carrier" condition would seem to offer, next to experimentation on anthropoid apes, the best means for the comparative testing of various immunizing preparations of the typhoid bacillus, designed to be used on man.

18. Forster and Kayser: Ueber das Vorkommen von Typhusbacillen in der Galle von Typhuskranken und "Bacillenträgern," München. med. Wchnschr., 1905, lii, 1473.

19. Possett: Atypische Typhusinfektion. Typhus ohne Darmerkrankung. Lubarsch and Ostertag: Ergebn. d. allg. Pathol., 1912, xvi, 184.

19. Richardson: On the Rôle of Bacteria in Gall-Stones, Jour. Boston Soc. Med. Sc., 1899, iii, 79.

AGGLUTINABILITY OF BLOOD AND AGAR STRAINS OF THE TYPHOID BACILLUS

*STUDIES IN TYPHOID IMMUNIZATION. II**

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The growth of the typhoid bacillus on an agar-medium containing 10 per cent. defibrinated rabbit blood, which we have found of advantage in our experiments, differs in certain respects from the growth on plain agar. We have already noted that the blood-agar cultures are more abundant. A concrete example of the amount of growth produced on each medium may be drawn from certain of our vaccine preparations to be more fully described later. To produce growths of *Bacillus typhosus* for immunizing vaccines we inoculate one-quart Blake bottles containing 100 c.c. of medium with a few cubic centimeters of a twenty-four-hour bouillon-culture of the organism. In one experiment nine Blake bottles of 2 per cent. agar were inoculated with a plain bouillon-culture of *B. typhosus* No. 3; at the same time, nine Blake bottles of 10 per cent. blood-agar were inoculated with a blood-bouillon culture of *B. typhosus* No. 3b. After incubation at 37 C. (98.6 F.) for two days, the collected agar and blood-agar growths were suspended each in 220 c.c. of normal saline, filtered through cotton and precipitated with 300 c.c. of absolute alcohol. After centrifugalization, the separate precipitates were again centrifugalized and dried over sulphuric acid for two days. These dried cultures were ground and weighed with the following results: Blood-growth, 0.675 gm.; agar-growth, 0.36 gm. It will thus be seen that the growth of the organism is almost twice as abundant on 10 per cent. blood-agar as on plain agar. Not only is the growth of the blood organism more abundant, but its morphology differs distinctly from the agar-strain. When examined in hanging-drop preparations, the blood-strain of the typhoid bacillus is larger, thicker and tends to grow in chains. It remains, however, quite as motile as the agar variety.

Associated with the morphological change that the organism undergoes when grown on rabbit blood, and we believe in some way dependent on it, are certain distinct and important variations in the agglutinability of these organisms by antityphoid serum. The ultimate identification of bacilli isolated from the blood-stream of suspected typhoid-carrier rabbits

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depends on their agglutination by means of a potent antityphoid serum. Our first attempt to agglutinate such a culture (*B. typhosus* 3a), which culturally and morphologically agreed with the characteristics of *B. typhosus*, with a potent antityphoid serum from the rabbit, was a complete failure. The rabbit furnishing this serum had been immunized by repeated inoculations of killed agar-cultures of *B. typhosus* suspended in saline and its serum agglutinated the stock cultures with which we were working in dilutions of from 1:10,000 to 1:20,000. The failure of this potent diagnostic serum to agglutinate the cultures derived from the suspected carrier in dilutions of 1:100, in view of the fact that these cultures were isolated on a blood-medium, whereas they had been growing on an agar-medium before inoculation into the rabbit, led us to suspect that we might be dealing with the phenomenon described by Bordet and Sleeswijk with the whooping-cough bacillus.

Bordet and Sleeswijk,[1] it will be remembered, found that the serum of an animal that had been immunized by injections of agar-growths of the Bordet-Gengou whooping-cough bacillus would clump similar agar-strains, but had no effect on blood-culture growths of the same organism. The serum of an animal immunized by means of the blood organisms would, however, agglutinate both varieties of whooping-cough bacilli. With these observations in mind we immunized several rabbits with blood-cultures of *B. typhosus*, and compared the agglutinating properties of their serums with the serums of rabbits that had received agar-cultures of the organism.

In Table 1 are groupted the results from a series of experiments with antiserums from rabbits obtained in the manner indicated. The first three serums in the vertical columns are from rabbits that had been given injections of agar-cultures of *B. typhosus;* the other six serums are from animals that received blood-cultures (*B. typhosus* 3a).

Table 1 shows clearly the following facts: An antityphoid serum from a rabbit that has been immunized by blood-agar cultures of *B. typhosus* has the property of agglutinating indiscriminately, to the limit of its potency, both blood and agar-cultures of the organism.[2] The serum of a rabbit immunized against agar-cultures agglutinates the agar organism only. The inagglutinability of blood-cultures by antiagar serum is not due to some property acquired in the living animal, as similar results can be obtained by simple subculture for two generations of the agar-strain on blood-medium. The agglutinability may be restored by retransference to the agar-medium. Growth in bile produces the same results as growth in blood.

1. Bordet and Sleeswijk: Séro diagnostic et variabilité des microbes suivant le milieu de culture, Ann. de l'Inst. Pasteur, 1910, xxiv, 476.

2. It may be noted, however, that the agglutination of the blood-strains invariably proceeds more slowly than that of agar-cultures.

The variation in the morphological appearance of the blood-agar cultures suggests that the failure of these organisms to agglutinate might be due to some physical difference acquired by growth on this medium. It is known that the agglutinability of members of the *mucosus capsulatus* group of bacteria, for instance, is dependent on the absence of a capsule.[3]

Two recent articles seem to prove that the typhoid bacillus may be capsulated either under exceptional conditions, or perhaps as a rule, provided proper strains are used. Kuhnemann[4] found capsules could be

TABLE 1.—LIMITS OF AGGLUTINATION OF AGAR AND BLOOD-AGAR STRAINS OF B. TYPHOSUS WITH SERUMS DERIVED FROM RABBITS BY IMMUNIZATION WITH AGAR OR WITH BLOOD-AGAR CULTURES

Strains of *B. Typhosus*	Antiagar Culture Rabbits			Antiblood Culture Rabbits					
	4	5	6	19	39	42	50	51	52
Agar 5	20,000	10,000	2,000	2,000	4,000	2,000	2,000	500	8,000
Agar 3	10,000	.....	.....	.....	.....	.....	.....	1,000	1,000
Blood 3a	100*	100*	100*	2,000	.....	2,000	1,000	1,000	500
Blood 3b	100*	.....	.....	.....	1,000	.....	.....	.....	1,000
Blood 3^2	100*	.....	.....	.....	1,000	.....	.....	.....	.....
Blood 3^3.	100*	.....	.....	.....	.....	.....	.....	.....	1,000
Blood 5^3	100*	.....	.....	.....	.....	.....	.....	.....	2,000
Bile 3	100*	.....	.....	.....	1,000	.....	.....	.....	.....
Bile 5	100*	.....	.....	.....	1,000	.....	.....	.....	.....

* Negative.

The figures indicate the highest dilutions of the serum at which a positive agglutination was obtained. The macroscopic method was uniformly employed, each tube containing a dilution of the serum in 1 c.c. of salt solution plus a uniform amount of the organism; in the case of the suspended cultures from blood or agar, this was obtained by standardizing the cultures to a uniform turbidity and using 0.1 c.c. The final result was read after the tubes had stood for two hours at room temperature and then over night in the ice-chamber. No doubtful or partial results are noted and the results were controlled by adding each suspension to salt solution (1 c.c.). The "bouillon-bile" cultures consisted in adding 1 c.c. of a forty-eight-hour culture on this medium to the serum dilution. In the left hand column are the cultures of *B. typhosus* tested in relation to their origin and the mediums on which they had been grown before being tested. "Agar 3" and "Agar 5" refer to the original strains employed. "Blood 3a" and "3b" indicate the Culture 3 passed through one or two carrier rabbits respectively; "Blood 3^2," "3^3," "5^3" indicates that the respective cultures had been simply transplanted from agar on the blood-medium for two or three generations with twenty-four hours between transplants. The bile cultures of five and three were subcultured twice on bile-bouillon before being tested.

3. Beham: Die agglutinatorischen Eigenschaften der Kapselbazillen, etc., Centralb. f. Bakteriol. 1912, Abt. I, Orig., lxvi, 110; Fitzgerald: Agglutination of Encapsulated Bacteria, Proc. Soc. Exper. Biol. and Med., 1912, x, 52.

4. Kuhnemann: Ueber Kapselbildung beim Typhusbazillen, Centralbl. f. Bakteriol., 1911, lvii, 497; Zur Identifizierung des Bacillus Faecalis Alcaligenes, Centralbl. f. Bakteriol., 1911, lvii, 469.

demonstrated by his modification of Loeffler's flagellum stains on typhoid bacilli that had been treated and clumped by fresh serum of young rabbits. He is inclined to regard this capsule formation as a protective mechanism on the part of the typhoid bacillus, as he found it only in such specially treated cultures. Carpano,[5] on the other hand, regards the failure hitherto to stain capsules on the typhoid bacillus as a purely technical matter, and he has succeeded in staining them on strains of the micro-organism on various culture-mediums.

Our own experiments with these stains have been convincing.[6] We had thought it might be possible to show capsules on the blood organisms with one of these stains while the corresponding agar-culture remained free, thereby indicating the correspondingly greater resistance to agglutination that is shown by the blood-strains. Such results, however, were not realized. With Kuhnemann's method the clear-cut capsules were found about all typhoid bacilli treated as he suggests with fresh young rabbit serum. We differ with him, however, in finding a considerable number of capsulated bacilli in twenty-four-hour preparations of both agar and blood-agar cultures. With Carpano's method we had no difficulty in demonstrating capsules on both the agar and blood-agar cultures. They are found surrounding each organism, clearly cut and uniformly. We have not succeeded, then, in demonstrating any structural basis for the differences in agglutinability of the agar and blood-agar strains of the typhoid bacillus.

It occurred to us that the relative inagglutinability of the blood-cultures might be due to the presence of some protective substance produced in the growth of these organisms. An attempt to prove this hypothesis by adding the supernatant extract of ground blood bacilli to agar-cultures resulted negatively; the agar-bacilli so treated were clumped as well as untreated bacilli by the antiagar-culture serum.

Absorption experiments have led hitherto to rather confusing results, the differences depending in the main on employment of more or less agglutinable strains of the bacillus. We prefer to reserve expression of opinion on this point to a later communication.

The practical interest of the relative inagglutinability of blood-strains of *B. typhosus* lies in its applicability of recently isolated strains of the micro-organism. In our preliminary communication,[7] we expressed the belief that freshly isolated typhoid bacilli which failed to respond to the characteristic serum test might respond more readily to an immune serum "obtained by immunizing animals with cultures grown on rabbit

5. Carpano: Ueber die Kapselhulle einiger Bakterien, Centralbl. f. Bakteriol., 1913, lxx, 42.

6. We are indebted to Miss Agnes Scholl for certain of these observations.

7. Gay and Claypole: Induced Variations in the Agglutinability of Bacillus Typhosus, Jour. Am. Med. Assn., 1913, lx, 1141.

(or possibly only on human) blood-agar." Such anticipation we have since been able to verify in practice.

It is a well-known fact among workers in diagnostic laboratories that cultures isolated from suspected cases of typhoid fever or from the stools of typhoid-carriers not infrequently fail at first of identification by their non-agglutinability with an antityphoid serum. Experience seems to vary as to the frequency with which such inagglutinable organisms are met. Thus Ledingham[8] says he has had little trouble in agglutinating fresh cultures from "carriers." Sawyer,[9] on the other hand, found that his eventually successful culture from a typhoid carrier on shipboard consisted in numerous colonies of organisms that biologically agreed with the characteristics of *B. typhosus*, but could not be finally identified by an agglutination test until they had been subcultured for ten to twelve generations on agar. Courmont and Rochaix[10] have studied hundreds of typhoid strains isolated from blood and stools of typhoid patients and also from dogs that had been given the dejecta of such patients. They state that many of these organisms are at first little agglutinable and do not become so until they have been subcultured in bouillon for ten to twelve generations.

Schiller[11] has found great variation in the agglutinability of suspected typhoid bacilli isolated from stools, some organisms from a given stool agglutinating readily with a strong antityphoid serum (titer 1 to 8,000), while others from the same stool failed to be clumped in a dilution of 1 to 100.

Kolle and Hetsch[12] state that very few real typhoid bacilli fail to agglutinate entirely, but that many agglutinate only feebly. Paltauf[13] states that the well-known failure of recently isolated typhoid cultures to agglutinate at best delays diagnosis and frequently leads to error.

Raubitschek and Natonek,[14] in a recent comparative study of strains of typhoid bacilli, express doubt of the absolute identity of some of their strains in view of the fact that some of them fail to agglutinate with a

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8. Ledingham: The Carrier Problem in Infectious Diseases, Longmans, Green & Co., London, 1912.

9. Sawyer: A Typhoid Carrier on Shipboard, Jour. Am. Med. Assn., 1912, lviii, 1336, and personal communication.

10. Courmont and Rochaix: Technique de la détermination du bacille d'Eberth par la recherche de l'agglutination, Compt. rend. Soc. de biol., 1910, lxix, 134.

11. Schiller: Beiträge zur Typhus-Epidemiologie, Centralbl. f. Bakteriol., 1908, xlvi, 385.

12. Kolle and Hetsch: Die experimentelle Bakteriologie, etc., Urban and Schwarzenberg, Berlin, edit. 3, 1911, p. 261.

13. Paltauf: Die Agglutination, Handbuch der pathogenen Micro-organismen, Kolle and Wassermann, Ed. 2, 1912, ii, 505.

14. Raubitschek and Natonek: Ueber Unterschiede in den biologischen Eigenschaften der Typhusbacillen, Centralbl. f. Bakteriol., 1913, I Abt., orig., lxix, 241.

strong antityphoid serum. It is interesting to note that their cultures have all been recently isolated from various organs of cadavers.

We have of late had the opportunity of examining three recently isolated typhoid cultures, one of which (D) was reported as failing to agglutinate with an antityphoid serum.

TABLE 2.—AGGLUTINATION OF FRESHLY ISOLATED STRAINS OF B. TYPHOSUS IN VARIOUS GENERATIONS WITH ANTIAGAR AND ANTIBLOOD IMMUNE SERUM FROM THE RABBIT*

B. Typhosus Culture Generations on Agar	Antiagar Agglutinating Serum 5†	Antiblood Agglutinating Serum 42
Stock 5	1 : 16,000 +	1 : 2,000
A 1	1 : 1,000	1 : 500
B 2	1 : 100	1 : 2,000
C 2	1 : 10,000 +	1 : 2,000
D 2	1 : 100	1 : 500
D 5	1 : 100	1 : 2,000
D 8	1 : 1,000	1 : 2,000
D 9	1 : 1,000	1 : 2,000
D 12	1 : 2,000	1 : 2,000

* Cultures tested: (A) From Dr. J. V. Cooke, University of California Hospital. Original culture from spleen (necropsy 1337, May 24, 1913). Kept on ice without subculture from May 27 to June 12; (B) From Dr. J. V. Cooke. Cultures from blood of patient furnishing culture A taken three days before death. One transplantation. Kept on ice from May 23 to June 12; (C) From Dr. J. V. Cooke. Blood-culture from Mrs. N. taken May 13, 1913. Second transplant. Kept on ice from May 15 until test June 12; (D) From Dr. E. Foster. These cultures were tested with both an antiagar culture typhoid serum from rabbit (5) and an antiblood culture typhoid serum from rabbit (42); the least agglutinable culture was repeatedly sub-cultured at twenty-four-hour intervals on agar until it became readily agglutinable by the antiagar as well as the antiblood serum.

† The plus sign indicates that the limit of agglutination was not reached in the given experiment.

Table 2 shows that the antiagar-culture serum 5 is the more potent, agglutinating the Stock Culture 5 in a dilution of 1 to 20,000 (Table 1). The antiblood-serum agglutinates the stock organism in a dilution of 1 to 2,000 only. Of the freshly isolated cultures, one only, C in the second transplantation, reacts like a stock culture of *B. typhosus* to an antiagar or the usual diagnostic serum. Culture A reacts relatively feebly to the antiagar serum so that diagnosis might be questioned. Cultures B and D react only in a dilution of 1 to 100, and it must be remembered that they were used first when in the second generation on agar. Even in this generation their diagnostic identification as *B. typhosus* could not be accepted. But the point of most interest is that all the organisms react strongly with the absolutely weaker antiblood-culture serum. The reaction of Culture B2 is particularly striking—diagnosis negative or at best doubtful with the antiagar-serum, but strikingly positive with antiblood-

serum, 1 to 2,000. The subsequent generations of D show how the growth on agar renders the inagglutinable organism susceptible to an ordinary rabbit immune serum obtained with agar-cultures.

The conclusion seems justified that the diagnosis of suspected typhoid bacilli can be rendered immediately certain even on first isolation by the use of an immune serum obtained by treating animals with cultures of the organism grown on blood. The application of this diagnostic procedure to other organisms such as *B. dysenteriae* (particularly of the Shiga type) would be interesting.

THE EXAMINATION FOR DIAGNOSTIC PURPOSES OF THE ENZYME ACTIVITY OF DUODENAL CONTENTS*

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Since the introduction of the duodenal tube by Einhorn[1] and by Gross,[2] this method of reaching the duodenum has been employed for a variety of purposes. It has been used to maintain nutrition in diseases of the stomach and other conditions,[3] to treat a variety of constitutional diseases by irrigation[4] and to secure fluid for a study of the bacterial flora of the upper intestine, and likewise the activity of the pancreatic enzymes and the detection of bile. Despite the many possibilities which have been opened by this method of entrance into the intestines, it would appear to have received attention only in a few circles. As a method of ascertaining the activity of the pancreas for diagnostic purposes, it is obviously more logical than the various indirect methods entailing an examination of the feces or urine.

The results which have thus far been obtained in the examination of duodenal contents deserve brief review. It has been shown by Hess[5] in infants, and more recently by MacNeal and Chace[6] in adults, that this method may be employed to excellent advantage in the study of the bacterial flora of this part of the intestines. MacNeal and Chace observed that, normally, when free hydrochloric acid was present in the stomach, the contents of the duodenum were comparatively sterile, but when free acid was absent, numerous organisms were present. In a case of typhoid which they had the opportunity to examine, typhoid bacilli were present in large numbers, while in an infant, aged 22 months, Hess made a similar observation.

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* From the Medical Service and the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital.

1. Einhorn: Med. Rec., New York, 1910, lxxvii, 98.

2. Gross: New York Med. Jour., 1910, xci, 77.

3. Einhorn and Rosenbloom: Am. Jour. Med. Sc., 1911, cxlii, 7; Einhorn: Post-Graduate, 1913, xxviii, 550; Hess, A. F.: The Use of a Simple Duodenal Catheter in the Diagnosis and Treatment of Certain Cases of Vomiting in Infants, Am. Jour. Dis. Child., 1912, iii, 133; Morgan: Am. Jour. Med. Sc., 1912, cxliii, 670.

4. Gross: New York Med. Jour., 1911, xciii, 171; Med. Rec., 1912, lxxxi, 706; Jutte: New York Med. Jour., 1912, xcv, 543.

5. Hess, A. F.: Jour. Infect. Dis., 1912, xi, 71.

6. MacNeal, Ward J., and Chace, A. F.: A Contribution to the Bacteriology of the Duodenum, THE ARCHIVES INT. MED., 1913, xii, 178.

The first paper of importance on the enzyme activity of the duodenal contents was that of Einhorn and Rosenbloom,[7] who studied the influence of various agents on the secretion and activity of the juice in a series of persons. In general, they were able to confirm the physiologic observations on animals. They noted that the secretion was active during fasting, while the administration of secretin, hydrochloric acid, pilocarpin, etc., caused an increased secretion of fluid, and generally a more active one. The activity of the juice in diseases possibly involving the pancreas was not considered.

Several very instructive papers on the examination of the juice in infants have appeared by Hess,[8] who conducted much of his work in the baby wards of this hospital. He observed that bile was rarely excreted during the first twelve hours of life, while in the subsequent twenty-four hours it was variable. In cases of marked jaundice it was observed to be profuse, the jaundice preceding the excretion of bile into the duodenum. The three pancreatic ferments were found in the infants before they had been put to the breast, and thus without the stimulus of food to incite the secretion. In older infants, a month or more of age, with the increase in the secretion of the juice, a decided increase in the amylolytic power was observed. The development of this starch-splitting enzyme so early in life is particularly interesting. In certain atrophic infants it was noted that, although they secreted little gastric juice to act as a stimulus, a very large amount of thin, watery juice containing all the pancreatic ferments, though weak in lipase, could be aspirated from the duodenum.

In a series of cases of adults without pancreatic disease, Frank[9] found active trypsin in all cases.

While the present work was in progress an interesting paper appeared by Crohn[10] on the diagnosis of the functional activity of the pancreatic gland by means of ferment analyses of the duodenal contents. His series included a number of cases of interest, namely one case of acute pancreatitis, three cases of obstructive jaundice, five cases of cholelithiasis and six of diabetes. In the case of pancreatitis, amylase and trypsin were found absent from the duodenal juice and likewise from the feces. The cases of obstructive jaundice showed an absence of bile, but a normal enzyme activity, except in one case, in which the amylase and trypsin

7. Einhorn, Max, and Rosenbloom, Jacob: A Study of the Duodenal Contents in Man, THE ARCHIVES INT. MED., 1910, vi, 666.

8. Hess, A. F.: A Study of Icterus Neonatorum by Means of the Duodenal Catheter, Am. Jour. Dis. Child., 1912, iii, 304; The Pancreatic Ferments in Infants, Am. Jour. Dis. Child., Oct., 1912, iv, 205. A Consideration of the Pancreas and Its Ducts in Congenital Obliteration of the Bile-Ducts, THE ARCHIVES INT. MED., 1912, x, 37.

9. Frank: Arch. Verdauungskr., 1912, xviii, 387.

10. Crohn: Am. Jour. Med. Sc., 1913, cxlv, 393.

were absent on the first examination. The duodenal juice in the cases of cholelithiasis and of diabetes was found normal. This observation in diabetes would appear to emphasize the point, sometimes misunderstood, that there is no disturbance of the external secretion of the pancreas in this condition.

A study of the enzyme activity of duodenal juice was begun more than a year ago. The objects of the investigation were (1) to establish the normal limits of variation in the activity of the pancreatic enzymes, (2) to ascertain the chemical composition and enzyme activity of the duodenal juice in a variety of pathologic conditions, (3) to determine what influence the gastric acidity might exert on the composition of the duodenal juice, and (4) to perfect methods of determining the admixture of bile by the estimation of the bile pigments and cholesterol. In view of the scant attention which the problem has attracted, we have thought it desirable to report the results which have been obtained in the examination of duodenal juice in thirty cases. It is planned to continue the study on interesting cases as they may arise.

METHOD OF OBTAINING DUODENAL JUICE

The technic employed in obtaining the duodenal juice has already been described by MacNeal and Chace.[11] A small soft rubber tube (external diameter of 3.5 mm.) capped with a perforated gold tip, is placed in the patient's mouth with instructions to swallow. With the patient lying on his right side, the tube is usually carried by the peristaltic waves of the stomach into the duodenum in about twenty minutes. Its position can be demonstrated either fluoroscopically or by examination of the aspirated contents. The tube is usually allowed to pass to about 80 cm. It was generally given at 10:30 p. m. and the duodenal contents aspirated with a glass syringe at about 9:00 a. m.; then with the tube still in place an Ewald test-breakfast was given and the duodenal contents aspirated one hour later. Occasionally the tube was passed at 7 a. m. and the duodenal contents aspirated at 9 a. m. This method is generally as accurate, and is more acceptable to the patient.

Duodenal Juice.—The duodenal juice obtained in this way is normally a clear or nearly clear, golden yellow, slightly viscid fluid. It is faintly acid, neutral or faintly alkaline in reaction to litmus and has a specific gravity of about 1.005. The juice contains bile as its color would indicate, and active amylolytic, lipolytic and proteolytic enzymes.

Methods of Examination.—The methods which have been employed in the examination of the duodenal juice are briefly described below. They are slight modifications of well-known methods which have been simplified in so far as possible for use in this connection. It was apparent in this work that the determinations of the enzyme activities were only relatively quantitative. On this account, and because of the small amounts of fluid often obtainable, a relatively simple technic has been employed.[12] With the technic described, complete data can be secured with 6 to 7 c.c. of juice.

11. MacNeal, Ward J., and Chace, A. F.: A Contribution to the Bacteriology of the Duodenum, THE ARCH. INT. MED., 1913, xii, 178.

12. These methods have been described by Myers and Fine: Essentials of Pathological Chemistry, New York, 1913, p. 25.

After securing the juice, it was taken to the laboratory without delay and placed in a refrigerator at 0 C., unless the examination was to be made at once. In the latter half of the present series this was the case. It is not believed, however, that refrigeration, at least for a short period, produces any appreciable change in the enzyme activity of the juice. It was very soon observed that little or no amylolytic activity could be demonstrated in a juice which was slightly acid to litmus, even though the juice had been at once neutralized when received. The proteolytic activity was affected in the same way, though to a much less extent. In the case of the lipase it was observed that the juice, which was faintly alkaline to litmus, always showed a weak lipolytic activity. It should be noted here, however, that the juice was not previously acidified. The initial reaction of the juice is obviously an important factor in the observed enzyme activity.

(*a*) *Reaction and Total Acidity.*—The reaction was ascertained with strips of red and blue litmus, while the total acidity was titrated with N/20 NaOh, using phenolphthalein as indicator, and employing as large amounts of material as might be available.

(*b*) *Amylase* (*Amylopsin*).—The Wohlgemuth method is simple and fairly satisfactory. Into each of six small test-tubes are introduced 5 c.c. of 1 per cent. soluble starch solution. Tube one serves as a control and to the remaining five tubes are added 0.05, 0.1, 0.25, 0.5, and 1.0 c.c. of the juice diluted one-half with distilled water. The tubes are then incubated at 38 C. for thirty minutes, immediately nearly filled with cold water, two drops of N/10 iodin added, and the tubes shaken. The tube is selected as positive which shows an entire disappearance of all blue color. The enzyme activity is expressed in the number of c.c. of starch solution 1 c.c. of undiluted juice is capable of digesting. If it takes 1 c.c. of juice to digest 5 c.c. of starch, the activity is five; if digestion is accomplished by 0.25 c.c., it is twenty, etc. For the five tubes as diluted above, the activity figures are 200, 100, 40, 20 and 10.

(*c*) *Lipase* (*Steapsin*).—Into each of two test-tubes are introduced 1 c.c. portions of the juice, one of which is boiled to serve as control. To each of these tubes are added 1 c.c. of neutral ethylbutyrate, 10 c.c. of distilled water and 1 c.c. of toluene. The tubes are shaken and placed in the incubator at 38 C. for twenty-four hours, shaking several times during the interval. At the end of this time they are removed to porcelain dishes and titrated with N/20 NaOH, using phenolphthalein as indicator. The titration result of the boiled tube is subtracted from the unboiled to obtain the figure for the lipolytic action.

(*d*) *Protease* (*Trypsin*).—Two methods have been employed, the O. Gross casein method, and a modification of the Fermi gelatin method. Casein has the disadvantage that it is also attacked by erepsin, though this is probably a negligible factor here, while the gelatin digestions must be carried on at room temperature.

Casein Method.—Into each of six small test-tubes, as in the amylase method, are introduced 5 c.c. of 0.1 per cent. pure casein in 0.1 per cent. sodium carbonate,[13] and the same amounts of duodenal juices added as in the case of the amylase. The tubes are incubated for fifteen minutes at 38 C. and then acidified with two drops of dilute acetic acid. The tube which remains perfectly clear, that is, in which digestion has been complete, is recorded. The tryptic activity is calculated in the same way as the amylolytic activity, except that the tryptic activity, according to the Gross formula, is an expression of the power of 1 c.c. of the juice on 10 c.c. of the casein solution, instead of 1 c.c., as in the Wohlgemuth method. The five tubes, according to the Gross scheme, represent activities of 20, 10, 4, 2 and 1, that is, one-tenth of the values obtained in the case of the amylase.

13. The soluble starch and casein solution were made up a liter at a time, a little chloroform and toluene added, and kept in a refrigerator at 0 C.

Enzyme Activity of Duodenal Contents Tabulated According to Gastric Acidity

Group I. Cases showing an absence of free hydrochloric acid

Case	Diagnosis	Gastric Acidity		Total Duodenal Acidity	Volume of Fluid c.c.	Condition §	Reaction to Litmus	Amylase	Lipase	Trypsin	
		Free HCl	Total Acidity							Casein	Gelatin cm.
1—B. A.....	Myxedema	0	6	5	14	F	Neutral	5	0.7	2	3.9
2—M. McG...	Chr. gastric ulcer.	0	8	8	19	F	Neutral	200	0.3	4	3.7
3—J. K.....	Asthenic gastritis.	0	10	10	5	F	Neutral	20	1.5	4	3.8
4—J. L.....	Pernicious anemia	0	20	9	20	F	Neutral	10	2.6	2	5.6
		..	..	..	15	F	.....	100	...	4	4.2

Group II. Cases showing an hyperacidity, the free HCl being above 25

5—I. S.	Gastric ulcer	50	77	12	20	F	Neutral	100	0.3	4	3.2
		..	..	10	6	E	Faintly alk...	100	0.3	10	2.1
		..	..	10	7	F	Faintly alk...	10	0.3	10	4.2
6—W. L....	Gastric ulcer	50	70	5	6	E	Neutral	100	0.4	4	4.3
7—C. L.	Gastric ulcer	50	75	..	5	F	Faintly alk...	100	0.3	4	3.1
		..	..	23	15	E	Faintly acid..	5	1.0	0	3.2
		..	..	25	6	E	Faintly acid..	0	1.0	0	5.3
8—M. P. ...	Hyperchlorhydria	30	70	10	10	F	Neutral	200	0.2	4	3.9
		..	..	..	2	E	Neutral	...	...	...	3.9
9—R. L.	Alcholic gastritis..	28	58	55	15	F	Acid	0	1.7	0	0.4
		..	..	75	13	E	Acid	0	2.3	0	...
		..	..	85	10	F	Acid	0	0.	0	...
		..	..	65	27	E	Acid	..	2.7	...	...
		..	..	35	10	F	Acid	...	1.5	...	4.2
		..	..	80	24	E	Acid	...	1.3	...	1.0
		..	..	80	25	E	Acid	...	2.8	...	0.7
10—S. W. ...	Neurosis	30	60	15	9	F	Faintly acid..	10	0.7	4	4.9
		..	..	10	27	F	Neutral	20	1.3	10	5.2
		..	..	..	4	E	Neutral	10	0.4	4	4.2
		..	..	10	23	F	Faintly acid..	0	1.8	2	3.5
11—T. B.	Duodenal ulcer ...	73	89	5	5	F	Faintly alk...	10	0.6	2	2.6
		..	..	15	15	E	Neutral	5	1.0	...	3.4
12—A. B.....	Gastric ulcer	90	105	0	40	F	Alkaline	2	0.3	10	4.8
	Gastro-enterostomy	..	..	0	20	E	Alkaline	40	0.3	10	4.5

Group III. Cases showing normal acidity

GROUP III. CASES SHOWING NORMAL ACIDITY

13—B. B.	Endocarditis	10	35	10	17	F	Neutral	40	0.3	10	2.8
		..	..	..	6	E	Acid	0	...	2	0.6
14—A. P.	Gastric ulcer	21	60	35	15	F	Faintly acid..	0	1.7	0.5	1.7
15—G. H. ...	Duodenal ulcer....	10	37	8	13	F	Faintly alk...	40	2.3	10	5.8
		..	..	13	10	E	Faintly alk...	40	2.1	10	4.7
16—B. D.	Gastroptoni	15	50	15	6	F	Faintly alk...	100	1.9	4	3.3
17—F. S.	Pulmonary and intestinal tuber....	20	35	13	15	F	Faintly acid..	5	3.1	4	3.7
		..	..	25	12	E	Faintly acid..	2	3.8	2	3.0
18—C. F.	Neuritis	30	54	10	10	F	Neutral	10	1.7	4	3.4
19—E. H. ...	Gastroptosis	24	56	5	10	F	Neutral	5	2.0	2	3.7
20—R. E.....	Gastroptosis	13	27	10	8	F	Neutral	...	0.9	...	3.6
		..	..	5	8	E	Neutral	...	0.9	...	3.1
21—A. O'C....	Arthritis deformans	8	16	..	3	F	Faintly alk...	40	...	4	3.6
		..	..	..	2	F	Faintly alk...	100	...	2	...
		..	..	5	19	F	Faintly alk...	100	0.6	4	4.4
		..	..	8	7	F	Faintly alk...	200	0.4	4	3.6
		..	..	8	9	F	Faintly alk...	40	2.2	4	4.5
		..	..	45	8	*	Neutral	100	2.0	4	5.4
22—S. Z.†....	Carcinoma of gall-duct and pylorus	17	53	..	5	F	Faintly acid..	0	...	4	3.1
		..	..	20	11	F	Faintly acid..	0	1.8	0.5	2.6
		..	..	15	9	F	Faintly acid..	0	1.6	2	3.2
		..	..	..	5	F	Faintly acid..	0	1.3	0.5	1.4
23—S. S.	Chronic pancreatitis, syphilis...	26	46	..	1	F	Faintly alk...	0	...	0	...
		..	..	4	26	F	Faintly alk...	0	0.6	0	0.0

GROUP IV. MISCELLANEOUS CASES

24—J. F.	Convalescent from pneumonia	..	..	20	12	F	Faintly alk...	40	2.9	10	3.0
		..	..	15	15	E	Faintly alk...	100	1.2	10	3.4
25—W. D. ...	Hypertrophic cirrhosis of liver..	..	..	3	10	F	Neutral	40	0.3	3	3.0
		..	..	3	3	E	Neutral	100	...	2	3.5
26—M. G. ...	Asthenic gastritis	12	30	5	10	F	Neutral	10	1.9	10	5.3
		0	12	5	8	E	Neutral	20	1.8	10	4.5
27—L. L.	Tuberculous pyelitis	..	..	10	20	F	Neutral	40	0.8	20	5.4
		..	..	10	10	E	Neutral	2	1.3	4	4.3
28—A. N. ...	Asthenic gastritis	4	14	5	10	F	Neutral	40	0.4	4	2.8
		..	..	..	2	E	.....	...	...	...	2.6
29—S. G.‡....	Acute infective jaundice	..	..	10	10	F	Neutral	100	0.1	1	4.3
30—J. O.....	Hypertrophic biliary cirrhosis...	7	32	7	16	F	Faintly alk...	100	1.8	10	4.5

* Test meal of milk, cream and boiled starch. † Bile absent from duodenal juice on each examination. ‡ Bile present in duodenal juice. § Fasting (F) or after Ewald meal (E).

Gelatin Method.—Into a small test-tube are pipetted 1 c.c. of undiluted duodenal juice, 3 c.c. of water, 1 c.c. of 0.5 per cent. sodium carbonate and 1 c.c. of toluene. Into the test-tube is then inserted two 3 cm. gelatin tubes,[14] and the test-tube allowed to incubate for forty-eight hours at room temperature with occasional gentle mixing. At the end of this time the amount of digestion is measured with a millimeter scale and the measurements added together.

(*e*) *Bile.*—The test employed for bile has been the simple Gmelin nitric acid test, though ordinarily sufficient bile is present to make a qualitative test unnecessary. In future analyses we plan to employ modifications of the Huppert test for bile pigments, and the Liebermann-Burchard test for cholesterol as the basis of colorimetric methods for estimating these substances.

The subjects of the present study were adults of an average age of about 35 years, sixteen being males and thirteen females.

DISCUSSION OF RESULTS

As may be observed from the tabulated data, the activities of the pancreatic enzymes show some little variation from day to day under normal conditions. Similar observations were made by Einhorn and Rosenbloom and by Crohn. The greatest variation was noted in the amylase and lipase, and was apparently dependent in part on the initial reaction of the juice. The favorable reaction for these two enzymes is quite opposite, neutral or faintly alkaline for amylase and faintly acid for lipase. The activity of the trypsin was more constant. In Patient 21 — A. O'C. — the tryptic activity was quite uniformly 4 over a period of several days, whereas the activity of the amylase varied from 40 to 200, and that of the lipase from 0.6 to 2.2. In the entire series, the amylolytic activity ranged from 5 to 200, the lipolytic activity from 0.3 to 3.8 and the proteolytic from 0.5 to 10 (casein method) and 1.4 to 5.6 (gelatin method).

It may be noted in Case 4 — J. L. — with pernicious anemia, that though there was an almost complete absence of gastric juice, the duodenal juice was very active, especially the trypsin (gelatin test). In Case 29 — S. G. — with infective jaundice, the lipolytic activity was very low, 0.1. The activity of the pancreatic enzymes was normal in the case of hypertrophic cirrhosis of the liver, 25 — W. D. In Group II, Case 9 — R. L.—with alcoholic gastritis, the juice was found to be strongly acid. This was believed at first to have been due to an error in technic, but the active lipase and the good digestion of gelatin on the one occasion when the acidity was comparatively low, would indicate otherwise. The results suggest an inability on the part of the pancreatic juice to neutralize the acid of the gastric juice. The results in Case 12 — A. B. — with gastric ulcer (gastro-enterostomy), are in striking contrast. Here the free gastric

14. The gelatin tubes were prepared by dissolving 10 gm. of gelatin and 1 gm. of sodium fluorid in boiling distilled water, deeply coloring with a clear solution of cochineal, making up to 100 c.c. and then filling glass tubing of 2 mm. inside diameter. The tubes 3 cm. in length are cut just previous to use.

acidity was 90 and the total acidity 105. The duodenal juice in this case was decidedly alkaline to phenolphthalein. The lipolytic activity was weak, but the proteolytic activity very strong. When this is considered, together with the large volume of juice obtained, it would appear to indicate that the pancreas had responded to the stimulus of the high gastric acidity. From the tabulated data it seems evident, however, that the acidity or lack of acidity of the gastric juice is without definite influence on the enzyme activity of the pancreatic juice, although a strongly acid gastric juice is apparently able in most cases to stimulate the production of a sufficiently alkaline duodenal secretion to neutralize it.

The normal variation in the activity of the pancreatic enzymes is so great, as evidenced by the data tabulated above, that only an absence of the enzymes would appear to render the juice of diagnostic value. The absence of pancreatic enzymes in the duodenal juice, would, however, be positive evidence of either pancreatitis or of non-potency of the pancreatic ducts, while the lack of bile in the juice would be pathognomonic of the occlusion of the common bile duct. By means of an analysis of the duodenal juice, the surgeon should in certain cases be able to determine the involvement or non-involvement of the pancreas prior to operating on the gall-bladder or gall-ducts.

In the case of chronic pancreatitis, 23 — S. S. — the enzyme activity of the duodenal juice was negative, except for 0.6 of lipase. The reaction of the juice was favorable for the detection of amylase and trypsin — faintly alkaline — and sufficient material, 26 c.c., was available for very careful examination. The stools were typical of pancreatitis. This coincides with the results obtained by Crohn in his case of pancreatitis, though it should perhaps be noted that there the fluid was acid.

In the case of carcinoma of the gall-ducts and the pylorus, 22 — S. Z. (diagnosis confirmed by operation)— the pancreatic ducts were not involved as shown by the active enzymes. (The absence of amylase was probably due to the reaction of the juice, faintly acid.) Bile could not be detected in any of the four specimens obtained.

CONCLUSIONS

Active amylolytic, lipolytic and proteolytic enzymes are present in duodenal juice, though the activity of these enzymes is apparently subject to considerable variation under normal conditions.

The acidity of the gastric juice appears to be without influence on the activity of the enzymes present in the duodenal juice.

In a case of carcinoma of the gall-ducts and pylorus with biliary obstruction, there was an entire absence of bile from the duodenal juice. In a case of chronic pancreatitis, the amylolytic and proteolytic activity was entirely negative, while the lipolytic activity was comparatively weak.

The absence of pancreatic enzymes from the duodenal juice would appear to be positive evidence of either pancreatitis or non-potency of the pancreatic ducts, while the lack of bile would appear to afford similar evidence of the occlusion of the common bile duct. Further observations on these conditions are desirable.

We desire to express our obligation and thanks to Dr. Edward Quintard, Director of the Department of Medicine, for permission to use the clinical material, and to Drs. B. Lattin and W. G. Lough for personal attention to details in collecting the specimens from the patients.

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II. HEMORRHAGIC DISEASE. ANTITHROMBIN AND PROTHROMBIN FACTORS *

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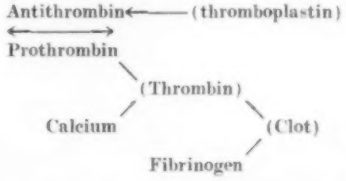
In a previous communication dealing with various types of hemorrhagic disease (Whipple[1]), we suggested that one factor, namely, antithrombin, might be of importance in various types of bleeding. The other elements of blood coagulation were taken up and some of the work on normal blood coagulation was reviewed. Because it is of great importance to have clearly in mind the mechanism of normal blood coagulation, it may be well to detail briefly Howell's[2] theory, as it seems to meet all the known requirements in the most satisfactory manner.



This shows in a schematic way the manner of blood coagulation. Howell believes that a small amount of antithrombin is present in the normal plasma and is sufficient to bind the prothrombin and render it inactive. Thromboplastin is set free by cell injury (blood-cells, platelets, tissues, cells, etc.), and neutralizes the antithrombin. This frees the prothrombin, which at once combines with calcium to form thrombin. The free thrombin coagulates the fibrinogen, giving the normal clot.

It is at once evident that this balance of antithrombin and prothrombin must be extremely delicate and capable of rapid adjustment. When the antithrombin accumulates in excess, the appearance of purpura and bleeding is to be expected, but if the antithrombin drops to a low level, spontaneous thrombosis might occur.

It is not surprising then that this very point seems to be the one about which most of the interesting cases of hemorrhagic disease may be grouped.

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* From the Hunterian Laboratory of Experimental Pathology, Johns Hopkins Medical School.

* Submitted for publication Oct. 17, 1913.

1. Whipple, G. H.: The Archives Int. Med., 1912, ix, 365.
2. Howell: Am. Jour. Physiol., 1910, xxvi, 453.

METHOD

Blood was obtained in all cases before death by means of a needle in a vein. The blood was aspirated into a solution of sodium oxalate (1 per cent.), the dilution being nine parts blood to one of oxalate. The blood from autopsy cases was usually obtained directly from the heart by means of a trocar and drawn into a bottle containing oxalate. Clear plasma was obtained by centrifugalization. In all experiments the calcium was supplied in the form of 1 per cent. calcium chlorid solution. The coagulation experiments were always done with the fresh blood plasma unless otherwise stated and the observation usually completed within two to six hours after the blood had been obtained. Control plasma from normal men, cats or dogs was always used fresh. Spleen extract was used only when fresh and made up by grinding the spleen with sand to a thin paste, adding sufficient salt solution and filtering through paper.

ICTERUS, LIVER DISEASE, BLEEDING

CASE 1.—Carroll. White male, aged 75. Admission July 11, 1912. Death July 20, 1912. Complaint, jaundice.

Family history negative. Past history negative, except strong alcoholic history up to 17 years ago.

P. I. Began April 19, 1912, with sudden appearance of jaundice which has been continuous ever since. On admission, skin was of a deep bronze color. The liver was definitely enlarged. There were marked hemorrhoids. Urine rich in bile. The general clinical picture suggested the diagnosis of cancer of the head of the pancreas.

July 12. White blood cells 12,100. Hb. 82 per cent. Stools contained no blood and were of acholic type. No evidence of bleeding.

July 13. No evidence of bleeding. Intense icterus. Blood drawn directly into oxalate from arm vein. (Table 1.)

TABLE 1.—CASE 1. COAGULATION TIME OF BLOOD IN JAUNDICE

Plasma C c.c	Plasma H c.c	Calcium Solution Drops	Coagulation Time Minutes
1	..	3	8
1	..	4	8
1	..	2	No clot
..	1	3	4
..	1	5	5

Plasma H is from a normal man. The slight delay of coagulation (Carroll) comes nearly within normal limits but may in view of later developments indicate a slight excess of antithrombin.

July 17. Red blood-cells 3,500,000. Hb. 70 per cent. W. B. C. 12,400. *Bleeding* was first noticed. There was oozing from the mouth, and blood-stained feces. Patient was in a low delirium.

July 18. Patient bleeding from mouth and there is some blood-stained vomitus. Blood is present in the stools and patient appears sick and is losing ground rapidly.

2:30 p. m. Blood drawn directly from vein into oxalate. This plasma showed an excess of antithrombin. (Table 2.)

TABLE 2.—Case 1. Second Experiment

Plasma C c.c.	Plasma D c.c.	Calcium Solution Drops	Coagulation Time Minutes	
			Start	End
1	..	3	14	40*
1	..	5	17	60*
..	1	4	3	3
2	1	15	3½	8
..	1	4	3	4
3	1	13	4½	11
1	..	2	26	..
1	..	1	26	..
1	1	7	5½	8-11*

* Clots wiped out often and subsequent clots formed slowly up to the final time. Plasma D obtained from a normal dog.

July 19, 9 a. m. The plasmas used on previous day were kept on ice. Fresh spleen extract made as usual. (Table 3.)

TABLE 3.—Case 1. Third Experiment

Plasma C, c.c.	Plasma D, c.c.	Spleen Extract Drops	Calcium Drops	Coagulation Time, Minutes	
				Start	End
1	..	..	3	35	..
1	..	4	3	3½	8-12
1	..	5	3	3½	6
..	1	6	5	1	..

Fresh spleen extract is rich in thromboplastin which can neutralize antithrombin with rapidity. It overcomes the slight amount of antithrombin in normal plasma and clots it in one minute, while the coagulation time of the antithrombin plasma is lowered to one-tenth its control. (Table 3, Case 1.)

July 20, 1 a. m. Death took place. Patient had been in a semistupor for the previous twelve hours. Temperature had been constantly subnormal.

1:20 a. m. Blood obtained directly from auricle and drawn into oxalate. The tests given below were performed immediately. Analysis shows the excess of antithrombin to have disappeared in great part, while the prothrombin has greatly diminished in amount. (Table 4.)

1. Blood drawn into clean bottle (no oxalate) began to clot slightly at edges after one and one-half hours; after twelve hours a flabby clot had formed all through the blood. After thirty-six hours in the ice box a tough clot had formed with retraction and escape of serum. There was no evidence of clot autolysis after three days.

2. Plasma C,[1] blood drawn into a clean bottle (no oxalate) and a few minutes later centrifugalized. Plasma a dirty orange yellow, slightly opalescent and rich in bile pigments. This plasma kept in a beaker free from blood cells showed a few filmy clots in one and one-half hours and thin clots on the wall of the

vessel after twelve hours, the center being free from clots. After twenty-six hours coagulation was not complete. At the end of three days a firm clot was formed.

3. Plasma C,[2] blood (Carroll) drawn into oxalate, centrifuged and preserved as usual — no clots formed.

4. Plasma D, oxalate plasma from a normal dog.

5. Spleen extract from the same dog, about twelve hours postmortem.

TABLE 4.—Case 1. Fourth Experiment

Plasma C,[1] No Oxalate c.c.	Plasma C[2], Oxalated, c.c.	Plasma D, Oxalated, c.c.	Spleen Extract Drops	Calcium Drops	Coagulation Time, Minutes	
					Start	End
1	.....	.....	.....	.....	30-60	
1	.....	.....	.....	2	40	
1	.....	.....	5	.....	35	50
1	.....	.....	10	.....	35	60
1	.....	*1	.....	.....	12	30+
.....	.....	1	7	5	½	½
1	.....	1	7	5	½	½
1	.....	.....	5	2	14	23
2	.....	1	.....	5	4	6
.....	1	.....	.....	5	50	.....
.....	1	*1	.....	3	6	

* Dog serum, which was twelve hours postmortem.

From an analysis of Table 4 we may conclude that the excess of antithrombin has completely disappeared from this blood, leaving only a small amount which may be within normal limits. The prothrombin has been greatly diminished, but has fallen not quite to zero, as the blood will clot in hours or days. This blood does not inhibit normal plasma coagulation. Spleen extract causes some acceleration of coagulation as does calcium, but the great deviation from normal consists in a great drop of the prothrombin content.

The spleen from this case was tested for its thromboplastin and found to contain very little of this element. Unfortunately, spleen extracts vary greatly in their thromboplastic activity, but it is possible that this organ had been depleted of its thromboplastin, which had been used in the neutralization of the blood antithrombin.

Necropsy No. 375½.—Anatomical diagnosis: Carcinoma of the head of the pancreas with complete occlusion of the common bile and pancreatic ducts; extreme icterus; dilatation of bile passages and gall bladder; cirrhosis and central necrosis of liver; dilatation of pancreatic ducts with chronic pancreatitis; metastases to the nearby lymph-nodes and liver; purpura, submucous, subserous and disseminated ecchymoses; gastric and intestinal hemorrhage; pulmonary ecchymoses, hemorrhage and edema; absence of blood clots in vascular system; general arteriosclerosis; emphysema of lungs; chronic adhesive peritonitis and pleuritis; caseous bronchial lymph-nodes; hypertrophy of prostate; slight chronic nephritis.

The body is that of a large white male, 161 cm. long. Rigor mortis is present. The skin everywhere has a deep icteric hue. The pupils are equal. There are indefinite purpuric splotches about the eye, at the bend of the elbow (blood culture) on the forearm and groin and over the flanks. Liver mortis is conspicuous. On incision the subcutaneous fat is pretty well preserved and of a deep yellow color. Scattered throughout the fat, over the abdomen particularly, are little hemorrhages. The abdomen on incision contains highly colored, orange-yellow, slightly turbid fluid (500 c.c. in amount). The small intestine is moderately dilated with gas and presents a mottled purplish appearance apparently due to blood either in the mucosa or lumen. The liver appears about 5 or 6 cm. below the costal margin and is deep green in color and presents several grayish nodules apparently a new growth. The gall-bladder is huge and slightly thickened, projecting just to the edge of the liver.

Thorax: The lungs are very voluminous, cushiony and cover over the heart. There are purplish flecks and splotches in the fat over the pericardial sac, the larger ones measuring 1 cm. The pericardial cavity contains a little bile stained, bloody fluid. The cavities of the heart contain no clots, and fluid blood runs out on section. The heart weighs 380 gm. Negative except for ecchymoses.

Spleen is large and soft, weighs 200 gm., measures 13½ x 8 x 4 cm. The capsule is irregular and roughened, specked with tiny ecchymoses and opaque yellow areas of thickening. There are extensive areas of thickening of the capsule near the hilum. On section the trabeculae are conspicuous. The blood-vessels stand open. The pulp scrapes off easily on the knife and is deep red, soft and velvety. The Malpighian bodies are very inconspicuous, ½ mm. in size.

The duodenum is intimately associated with the hard mass which appears to occupy the region of the head of the pancreas. There are extensive areas of purpura in this region. The lesser peritoneal cavity is partially obliterated by adhesions binding the firm nodular pancreas to the region of the pylorus, gastric and hepatic omentum, as well as the posterior wall of the stomach. On dissecting out the common duct it is found to be enlarged and thickened forming a tube about 3½ cm. in diameter, just outside of the wall of the duodenum. The enlarged gall-bladder measures 6½ cm. in diameter and 14 cm. in length. It is quite tense as is the common duct and distended. The cystic duct where it opens into the common duct measures about 1 cm. in diameter. The gall-bladder contains inky, black, slimy, stringy material and no calculi.

The stomach contains slimy fluid material. Its mucosa has undergone some post-mortem digestion. Ecchymoses, however, are numerous and easily made out. The orifice of the bile papilla is quite conspicuous, nodular and hard. There are two purplish projections about this papilla, one about the site of the opening of the lesser pancreatic duct. The head of the pancreas is of almost stony hardness and the growth seems to form a part of the wall which occupies the position of the bile duct. Section through the body of the pancreas shows a greatly dilated duct measuring 8 or 9 mm. in diameter. In the distal third of the organ the parenchyma is gray, translucent, very hard and firm, evidently in a condition of extreme chronic pancreatities with atrophy. No evidence of new growth. It is embedded in a thick layer of retroperitoneal fat. About the middle part of the pancreas it seems as though some of the tissue is replaced by a new growth, the tissue being grayer and more granular than the pancreatic tissue. Section through the head of the pancreas and papilla shows a continuous growth of new tissue replacing all the normal parenchyma.

The liver weighs 2,150 gm., measures 26 x 21 x 9 cm. The surface is rather irregular, due to the presence of gray nodules, some scarcely visible, other larger ones, 2 or more cm. in diameter. The larger ones are, as a rule, associated with more or less hemorrhage. Many of them are umbilicated. They are firm to the touch. The liver tissue elsewhere has a slaty green color. On section the liver parenchyma presents a nutmeg architecture, deep green alternating with opaque gray areas, the latter being about the portal spaces. Tumor nodules of all

sizes are scattered thickly over the section. The larger ones show central degeneration and necrosis. Some of the largest show softening associated with hemorrhage and digestion of the tissue, giving rise to cavity formation in the nodule.

Intestine: The jejunum shows a mucosa coated with currant-red, blood-stained mucus. Ecchymoses, however, are not numerous here, and this blood in great part came from the stomach and duodenum. Low in the jejunum, however, are a few scattered ecchymoses 2 to 3 mm. in diameter in the submucous tissue. The ileum is practically free from ecchymoses except occasional ones in the submucosa. The large intestine shows a similar picture and contains a large amount of semifluid, blood-stained, fecal material. The other organs need not be described.

Microscopical Sections.—The lungs show hemorrhage into the alveoli with a good many polymorphonuclears, but no fibrin anywhere. In the spleen phagocytes containing old blood pigment are numerous. Marrow of femur shows little hyperplasia; phagocytes, as in the spleen, are numerous.

Kidney: Slight chronic nephritis. Glomeruli and tubules distended with granular, albuminous fluid. Some hemoglobin casts are found.

Liver: Moderate grade of portal cirrhosis with reaction of bile ducts and new formed strands of cells. The bile canaliculi are enormous and dilated with brown colloid material. The cancer nodules are associated with the portal structures. The central cells of many lobules show necrosis and there is no cellular reaction about these dead liver cells. In some areas pigmented phagocytes are crowded into the capillaries, perhaps the result of repair of preceding liver injuries.

There is abundant evidence of a progressive injury, inflammatory reaction and repair of the liver lobules. The large tumor nodules show extensive hemorrhage, but no fibrin in any section examined.

ICTERUS AND HEMORRHAGIC DISEASE (CASE 1)

There is much confusion about icterus and true hemorrhagic disease. The preceding case is a true example of jaundice and bleeding. It is familiar to all that a slightly delayed coagulation time is frequently associated with icterus, but such cases may be operated on with no danger and calcium will bring the coagulation time back to normal. We have suggested that this may be due to a binding of calcium by the bile pigments, a compound which is broken up with difficulty, and this renders the calcium slowly available for coagulation.

True hemorrhagic disease is rarely associated with obstructive jaundice, although the surgeons are fearful of this combination and often make a mistaken diagnosis. Calcium has no effect on this condition. For the past two years many cases of severe icterus have been examined, as a hemorrhagic tendency was suspected, but the case above is the only one of the series which showed true hemorrhagic disease.

It is of interest that we can follow the sequence of events in this case during the last week of life, while the patient developed this hemorrhagic tendency. The patient, in spite of intense icterus, of months' duration, showed no bleeding tendencies one week before death, and a blood with normal coagulation factors, except possibly a slight excess of antithrombin. Four days later true hemorrhagic symptoms appeared, which were due to an excess of antithrombin demonstrated in the blood.

The blood obtained a few minutes after death showed only a slight amount of antithrombin—perhaps a normal amount—but a great drop in prothrombin, which caused great delay in blood coagulation.

This wide fluctuation of antithrombin and prothrombin is of much interest as they may be more or less interdependent. There is some evidence that antithrombin is produced in the liver. Under certain conditions and in certain diseases (melena neonatorum —see below) this element may quite disappear from the blood, but study of such cases gives no clue to the origin of prothrombin.

Here we are dealing with a disease-complex in which surely the hepatic changes are conspicuous and probably most important from the standpoint of abnormality of blood coagulation — intense and long-standing icterus with great widening of the bile canaliculi and obvious embarrassment of these liver cells; cancer metastases with rapid invasion and destruction of parenchyma; liver cirrhosis of a moderate grade with new-formed cells and abortive bile-ducts; central liver necrosis of some days duration judging from the cell-picture, yet free from the usual invasion by wandering cells. Surely this is a liver laboring under difficulties and reacting to injury in an abnormal way. There is no good reason why such a liver could not produce an excess of antithrombin. Experiments have shown that various stimulants (peptone, thrombin, etc.), which produce an excess of antithrombin in the blood, will not do so if the liver is excluded; in other words, the antithrombin excess may be produced wholly within the liver. Moreover, there is evidence from certain experiments done in this laboratory that antithrombin is being constantly formed as it is used up and is furnished in great part by the liver.

When parenchyma cells are killed in the body, we may presuppose an escape of considerable amounts of thromboplastic substance. This must be neutralized by the antithrombin or by some other agents to prevent rapid intravascular clotting. Necrosis of liver cells presumably would free an excess of thromboplastin and necessitate its neutralization. In this case we have an excess of antithrombin which vanished during the time when liver necrosis developed. May we not conclude, then, that in this instance the antithrombin excess was removed or rendered inert by the thromboplastin which escaped from the necrotic liver cells?

The terminal drop in prothrombin tempts speculation, but it may be best to refrain. At least there is a possibility that the liver is concerned in the elaboration of this substance, prothrombin, which is so elusive. The prothrombin-antithrombin balance is so delicate and its constant maintenance so important to the organism that more than one organ may be concerned in the equation, as seems to be the case with fibrinogen (Goodpasture[3]).

3. Goodpasture: Am. Jour. Physiol., January, 1914.

TYPHOID (?) LIVER DISEASE (?) BLEEDING—RECOVERY

CASE 2.—Schwab. Medical No. 29,842. White male, aged 56. Admission Oct. 26, 1912. Recovery.

F. H., negative. P. H., typhoid fever at 19. Patient in bed ninety days. Various attacks of malaria for the previous fifteen years. History of moderate alcohol. Gonorrhea twenty-five years ago. Denies lues.

P. I. began October 12 with shaking chills and sweats. Since then patient has suffered from general weakness.

October 26, red blood-cells 4,448,000. White blood-cells 12,600. Hb. 75 per cent.

October 28. Widal suggestive. Blood culture negative.

October 30. Temperature has been steadily elevated between 101 and 103 F., giving a typhoid-like curve. Liver enlarged and smooth. Spleen not felt. White blood-cells 15,000. Blood smears negative. Wassermann negative.

November 2. *Bleeding* from the gums first noticed. Temperature falling gradually. Clinical diagnosis, typhoid fever.

November 3. Bleeding from gums quite marked. There are numerous subcutaneous hemorrhages. One measures 3 cm. in diameter over the deltoid. Icterus noted in the subcutaneous tissue. Red blood-cells 3,512,000. W. B. C. 10,480. Hb. 65 per cent.

November 4. Bleeding time estimated at thirty-four minutes and several hours later at eigheen minutes. Coagulation time seven minutes and forty seconds.

November 5. Stools contain blood. Bleeding from gums continuous. Jaundice quite evident. W. B. C. 9,000. Liver palpable 6 cm. below the costal margin. There are definite areas of purpura around ear pricks and abrasions in skin. Blood drawn directly into oxalate from arm vein (see Table 5). The analysis of this table shows a definite *excess of antithrombin.*

TABLE 5.—CASE 2. COAGULATION TIME IN TYPHOID FEVER

Plasma H, c.c.	Plasma D, c.c.	Serum D, c.c.	Spleen Extract Drops	Calcium, Drops	Coagulation Time, Minutes	
					Start	End
1	.....	.....	.....	5	20	*30+
1	.....	.....	.....	4	17	*30+
1	.....	.....	6	4	.....	3½
1	.....	.....	12	4	.....	2½
.....	1	.....	.....	5	.....	6
2	1	.....	.....	14	7	*20+
.....	1	.....	6	5	.....	1½
1	.....	1	.....	.....	3	
.....	1	1	.....	.....	3	

*Clots formed slowly, wiped out and continued to reform. Plasma D, Serum D and spleen extract (weak) all fresh and obtained from a normal dog.

November 6. Purpuric spots are numerous. The gums continue to ooze blood. Widal with paratyphoid negative. Hb. 38 per cent.

November 7. Hb. 30 per cent. Bleeding stopped during the day. Blood obtained as usual tested by Dr. Howell showed normal elements of coagulation. The excess of antithrombin had disappeared.

November 12. Hb. 45 per cent. No more bleeding. Widal negative.

November 19. Hb. 48 per cent. W. B. C. 7,560. Temperature had been normal, but rose to 102.4 F. and remained elevated for ten days (relapse?). Thorax negative. Spleen palpable, but not greatly enlarged.

November 21. Blood culture and Widal negative.

November 24. Hb. 50 per cent. W. B. C. 3,400.

Dec. 22. Patient discharged in good health. Liver at this time still large and quite firm.

Clinical Diagnosis: Typhoid (?) followed by relapse. Enlarged liver.

This blood-plasma shows the characteristic slow coagulation associated with antithrombin excess. The soft clots may be removed (wiped out with a glass rod) every few minutes and other clots will reform, the process being repeated until the fibrinogen is all used up. This human plasma delayed the coagulation of normal dog plasma, in which we note again the slowly-formed clots and reformation after removal. Spleen extract which is rich in thromboplastin accelerates the coagulation to less than normal, but clots normal plasma in one and one-half minutes. It acts by neutralizing the antithrombin present. Fresh normal dog serum clots human and dog plasma alike in three minutes, indicating that this antithrombin does not retard the action of preformed thrombin on fibrinogen.

It is of interest that within a few days the hemorrhagic tendencies had vanished and blood examination revealed normal elements of coagulation. One is tempted to speculate on this transient upset of the antithrombin-prothrombin balance, and especially its *spontaneous return to normal*. As no treatment by serum, etc., was given, we are not confused by this factor, and do not hasten to credit this to the treatment. There is no reason to suppose that serum injection would be of value in such cases, as we are dealing not with a lack of any blood element, but with an excess of a normal constituent which is normally held in check by some mechanism not at present clear to us. If the antithrombin is formed by the liver and constantly used up, as some experiments indicate, it is proper to suppose that under certain conditions of liver disease or injury there may be an over-production of this substance. This case had an enlarged liver associated with an obscure infection, but unfortunately we cannot report on the anatomical changes present in the liver.

MILIARY TUBERCULOSIS—EPISTAXIS

Case 3.—King. Autopsy No. 3751. Black male, aged 39. Admission June 27, 1912. Death July 12, 1912.

P. H. Patient gave history of syphilis and there was a strong alcoholic history. Patient lost weight from 149 to 100 pounds. Three months prior to admission patient bled profusely from the nose, and had such attacks with considerable frequency. Patient complained of bleeding from nose and swelling of abdomen.

P. E. Indicated probable enlargement of liver and spleen. There was no purpura. Jaundice not noted. Skin pricks bleed freely. Bleeding time seven minutes. Red blood-cells 1,900,000. W. B. C. 1,000. Hb. 26 per cent. Patient

had profuse epistaxis during the day, perhaps amounting to 200 c.c. This was checked with difficulty.

June 28. Blood aspirated from arm vein directly into oxalate. This blood plasma clotted in a normal manner in four minutes on the addition of calcium. The clot retracted to a small volume and showed no digestion after twenty-four hours. *Fibrinogen* much below normal (.083 gm. per 100 c.c.—normal 400 gm.). This suggested some liver injury.

June 30. Patient had profuse epistaxis (100 c.c. ±) which was checked by packing. Hb. 27 per cent. White blood-cells 1,100.

July 12. Epistaxis and definite bleeding from the gums. Urine constantly negative. Temperature showed an up and down curve from 99 to 102.5 F. Death 5:30 a. m., associated with copious hemorrhage from nasopharynx.

Necropsy.—No. 3751. Anatomical diagnosis: Tabes mesenterica; tuberculous involvement of thoracic duct; general miliary tuberculosis; acute splenic tumor; ascites.

Body is that of an emaciated colored man, 146 cm. long. The pupils are equally dilated. Rigor mortis is marked. There is edema of the ankles and feet. Abdomen is slightly distended, and half way between umbilicus and pubis there is a scar (recent paracentesis). The chest is slightly barrel-shaped. On opening the abdomen it is found to be distended with clear straw-colored fluid, but no fluid is found in the pleural or pericardial cavities. There is great enlargement of the mesenteric lymph-nodes, which vary in size from that of a marble to that of a hen's egg. They are whitish in color, firmly bound to each other and to the vertebral column. The transverse colon and one or two loops of small intestines are also tightly bound to the mass. The whole mass measures roughly 25 x 15 cm. The heart and lungs are normally placed and no adhesions of the pleura are found.

Heart negative. Lungs show congestion, edema and numerous tubercles.

Spleen weighs 620 gm. It is enormously enlarged, and retains its shape very well. The capsule is smooth, glistening and free from adhesions. It is very firm in consistence and of a dark purple color. On section the same color is observed, but it is seen to be thickly studded with great numbers of minute yellowish grains. These are small and almost invisible but are uniformly distributed throughout the whole organ. The trabeculae are not well seen, apparently being widely separated by the increase in the pulp.

Liver weighs 1,500 gm., measures 25 x 19 x 6 cm. The surface is smooth, free from adhesions, yellowish brown in color and mottled with a few dark reddish areas. On section numerous small, yellowish tubercles are found scattered throughout the whole organ. There is also a slight increase in connective tissue. The lobulation is fairly distinct. Gall-bladder normal.

Microscopical Notes.—Lungs filled with small areas of tuberculosis which are of the exudative type. There is little connective tissue reaction and few giant cells. Edema is well marked.

Spleen is a mass of small tubercles. The reaction is chiefly exudative, the large and small mononuclears being chiefly concerned. Necrosis and degeneration are striking. Kidney and adrenals show tubercles.

In the liver small tubercles with much necrosis are very numerous; the liver cells show much atrophy and fatty degeneration. Other organs are negative.

Blood Examination.—July 12, 8:30 a. m. (three hours after death) blood drawn directly from right heart into oxalate. A few filmy clots had formed, but the fibrinogen analysis showed 110 gm. per hundred c.c., which excludes coagulation of any appreciable amount. See previous analysis.

Blood drawn directly into a clean bottle with no oxalate starts to clot within thirty minutes, forming filmy masses on the side of the container. After removal of this filmy clot, secondary clots form slowly. There was some tendency towards digestion of the formed clot after twenty-four hours. Plasma D obtained from normal dog. (Table 6.)

These observations are incomplete, but indicate pretty conclusively a slight excess of antithrombin in the blood at time of death. This is one of the few cases observed by us in which there was evidence of *clot digestion* after complete coagulation. We have seen two cases in which this clot digestion or fibrinautolysis was the essential factor in the complex and probably accounted for the prolonged and fatal bleeding. More study of such cases is needed before a report can be made.

TABLE 6.—CASE 3. COAGULATION TIME OF BLOOD AFTER DEATH

Plasma H c.c	Plasma D c.c	Calcium Drops	Coagulation Time Minutes	
			Start	End
1	..	5	12	12+
1	..	5	10	12+
2	1	14	7	8
..	1	5	5	6

It is to be remembered that this case did not have outspoken symptoms of hemorrhagic disease, only periodic attacks of profuse epistaxis, and during the last day of life some oozing from the gums. The fibrinogen of the blood was quite low, and this would favor prolonged bleeding from any small wound or abrasion of the mucosa or vessels. A similar condition may be met with in liver cirrhosis with profuse gastric hemorrhage and low fibrinogen content. The blood-clots in such cases are too flabby to seal the ends of the injured vessels.

This case probably belongs in the group of antithrombin bleeders associated with a septicemia. Two weeks before death there was a normal blood coagulation, but later an excess of antithrombin appeared and was a factor in the oozing from the gums and epistaxis. The body was full of small, rapidly-growing miliary tubercles associated with much cell necrosis and tissue destruction. It may be argued that the split products from this dead protoplasm were absorbed, carried to the liver where they caused stimulation and over-production of antithrombin. The liver itself was diseased and filled with tubercles, which process of itself may have actuated this over-production.

GENERALIZED THROMBOSIS — ANTITHROMBIN EXCESS

CASE 4.—Dean. Autopsy No. 3823. Baby born November 20 after difficult labor necessitating high forceps operation. Chloroform anesthesia thirty-five minutes. Mother recovered well. Placenta examination showed normal tissue. Weight of infant fell continuously from 4,070 to 3,130 gm. on the tenth day. Temperature rose to 101.5 F. on the third day, but fell to normal shortly after. On tenth day of life the baby showed retraction of neck, nystagmus and twitching of the extremities. During the next three days these symptoms diminished considerably but the general condition was very poor.

On the thirteenth day after birth an abscess of left cheek was opened. At this time a discoloration of finger tips of left hand and toes of left foot was noted. This suggested beginning gangrene. Child grew gradually worse and died December 5, 2 a. m. Body placed in ice-box until time of autopsy. Clinical impression: Septicemia; meningitis; gangrene.

December 6, 11 a. m. Autopsy performed thirty-three hours post-mortem. Blood in heart and large vessels was quite fluid; no clots. This blood clotted readily in contact with the cut tissues. Some of it collected in a test-tube showed no clot at the end of two hours but a firm normal clot at the end of twenty hours.

Necropsy.—Abstract of Protocol 3823.

Anatomical Diagnosis: Multiple thromboses involving umbilical vein, hypogastric arteries and external iliacs, ductus Botalli, aorta and portal vein; aneurysm of ductus Botalli; subdural hemorrhages posterior to cervical cord; slight internal hydrocephalus; pseudo-infarct of liver; fatty degeneration of viscera; atelectasis; bronchopneumonia.

Body is that of an emaciated, colored baby two weeks old, 50 cm. in length. Rigor mortis is present. The stump of the umbilical cord appears normal. There is an abscess on the left cheek from which exudes bloody pus on pressure. The left foot and ankle are of a deep purple color. On section abdomen appears normal. The peritoneal surfaces are smooth and glistening. The mesenteric lymph-glands are injected and seem slightly enlarged and in places hemorrhagic. Thymus is normal. The pericardial sac contains a normal amount of fluid. The surface is smooth and glistening. The lung surface shows many deeply injected areas varying from 1 to 2 cm. in diameter. On section they are air-containing for the most part, but a few reddish, slightly elevated areas are to be found.

The spleen is rather soft and grayish in color. The Malpighian corpuscles can be seen as minute grayish dots. Stomach and duodenum are normal. The bile ducts are patent.

Liver: On the anterior surface of the left and the middle portion of the right lobe is an irregularly outlined area measuring 4½ x 5 cm. which is deep purple in color. On section the purple area above described is definitely outlined and contrasts sharply with the adjacent tissue. It is of a reddish purple color with indistinct lobulation. The parenchyma elsewhere has a yellowish, opaque cast. The portal vein at the hilus and extending into the substance of the liver is occluded by a thrombus.

The intestines are injected. On opening the aorta a thrombus is found beginning 1 cm. above the bifurcation and extending down into both iliacs, on the left to the opening of the epigastric artery; on the right about 1 cm. below the opening of the right hypogastric artery.

The brain is found to be edematous and the vessels injected, and an excess of fluid flowed from the ventricles. The pia is otherwise normal. On section the lateral ventricles are somewhat dilated. On the posterior surface of the cervical cord is found a clot which covered an area 3 cm. in length. The clot appears recent. Other organs need not be described.

Microscopical Notes.—The vessels in some instances show thrombi which are partly organized. Lungs show some interstitial pneumonia somewhat like that seen in congenital syphilis. The alveoli contain an albuminous exudate and many alveolar cells but no fibrin. Some sections show extreme atelectasis. The capillaries of the liver are free from blood islands and there is no evidence of syphilis. Each lobule shows a central fatty degeneration involving about half the parenchyma. Pancreas and other viscera are normal. There is no evidence of syphilis.

This case, although incomplete, evidently presented an excess of antithrombin in the blood at time death. There may have been a low prothrombin fraction, but the great acceleration of coagulation of the

blood in contact with the cut tissues speaks against this. We may assume with some certainty that this case showed an upset of the antithrombin-prothrombin balance, and this is of interest chiefly because of its association with extensive vascular thrombosis. This infant probably was suffering from a general infection and the antithrombin excess may be classed with that found in severe septicemia and reported previously (Whipple[1]).

In this instance we believe the excess of antithrombin is in part dependent on extensive thrombus formation. Under such conditions the production of *thrombin* must be considerable, and its escape into the blood-stream inevitable. The introduction of thrombin into the blood-stream causes a transient rise of antithrombin as can be studied in the dog (Howell[4]). When a thrombus is developing slowly in the blood-stream we may assume a steady escape of thrombin and more or less elevation of the antithrombin curve. It may not be far from the truth to think of this antithrombin wave as a process tending to delimit the growth of any thrombus. We may consider this antithrombin reaction under these conditions as protective and tending to stop thrombus development. It will be of interest to follow this antithrombin curve in patients where there is some certainty of a progressive thrombosis or even an endocarditis of the malignant type. It is more than likely that there may appear periods of low antithrombin blood content which would favor the start or growth of a thrombus.

APLASTIC ANEMIA, PURPURA, BLEEDING, ANTITHROMBIN

Case 5.—Rykowski. Autopsy No. 3724. White male, aged 16. Admission April 3, 1912. Death May 6. Patient complained of faintness.

Present illness began nine weeks before death with epistaxis and bleeding of gums. Definite yellow color in skin noted one week before this.

April 3. Red blood-cells 796,000, white blood-cells 2,200, Hb. 15 per cent. Differential count showed small mononuclear leukocytes 83 per cent. Polymorphonuclear leukocytes 14 per cent. Myelocytes 2½ per cent. Blood clotted in five minutes, but the bleeding time was over twenty minutes. Examination of the eyes showed a definite retinitis with extensive hemorrhage. Sclerae pale and white.

April 10. *Strongyloides stercoralis* found in considerable number in stools. Wassermann negative.

April 16. Bleeding time very much prolonged and gums ooze blood constantly. Hemoglobin has fallen to 10 per cent.

April 17 patient was given an *indirect transfusion* of 500 c.c. defibrinated blood obtained from brother. Shortly after it his temperature rose to 105.6 F. accompanied by a chill.

April 18. Purpura noted in skin and mucous membranes of tongue. Epistaxis started and continued in spite of epinephrin.

April 19. Epistaxis with slow oozing continued. Blood culture and Widal both negative. Hb. 22 per cent. Red blood-cells 1,224,000. W. B. C. 1,280. A few blood platelets were noted.

4. Personal communication.

April 21. Hb. 17 per cent.

April 27, Hb. 12 per cent. Bleeding continued.

May 3, Hb. 9 per cent. Epistaxis and oozing continued.

May 5, respirations slow and deep. Fresh patches of purpura noted. Urine free from bile, urobilin and albumin. Temperature continued uniformly between 99 and 100.1 F. during the previous few days.

May 6, 12:05 p. m., death. Blood aspirated from heart directly into oxalate at 1:30 p. m.

Anatomical Diagnosis.—Hemorrhage in the subcutaneous tissues, pericardium, submucous tissues of the trachea, stomach, intestine and lungs; pericardial effusion; marked anemia; fatty degeneration of heart muscle; tuberculous bronchial lymphadenitis; chronic pleural adhesions; rectal polyps; adenoma of liver; bronchopneumonia with necrosis; central liver necrosis.

Necropsy.—Body is that of a very well nourished, white boy, 152 cm. long. The skin is waxy in appearance. The mucous membranes are extremely pale. There are a few small, purpuric spots over the right side of the forehead and elsewhere over the face. There is an excoriation on the left side of the nose and one on the upper lip. A few small ecchymoses over the arm and fading ones elsewhere on the body. These are not conspicuous below the waist except for a rather large conglomerate area on the right leg. Rigor mortis is well marked. The abdominal viscera are normally disposed and serous surface normal. The liver and the rest of the organs are extremely pale. The mesenteric lymph-nodes are large and firm. Sections, yellowish-gray in color, homogeneous in consistence. The thymus is fairly prominent and extends down over the upper part of the pericardium. It contains a great deal of fat. The pericardial surfaces both parietal and visceral are covereed with hemorrhages of various sizes from that of a pin-head up to several millimeters in diameter, flame shaped or streaked.

Liver measures 24 x 15 x 7 cm., weighs 1,200 gm. Gall-bladder contains thick, viscid, black bile. The edge is fairly rounded. The color is pale. On section the lobulation is indistinct but regular.

Bone-marrow is firm and yellowish in color, made up almost entirely of fat. There are only a few red specks representing clumps of bone-marrow cells.

Microscopical Sections.—Lungs: Areas of bronchopneumonia in which colonies of bacteria are conspicuous. There is much cell necrosis in these areas and fibrin threads are very numerous. Evidently the cell necrosis freed sufficient thromboplastin to neutralize the excess of antithrombin in the blood. One of the large vessels in an area of necrosis contains a small clot in which the fibrin is confined to the margin of the vessel.

Spleen: Malpighian bodies normal. Pulp contains little blood and the venules show slight thickening of their walls. No pigment. Lymph-nodes are negative.

Bone-marrow made up of fat cells. There are two or three clumps of normal marrow cells numbering six to twelve — complete aplasia.

Duodenum shows evidence of old hemorrhage into the villi, where are found numerous phagocytes containing yellow granular pigment.

Liver: The cells show slight increase in the fine, yellow, intracellular pigment. There is a central necrosis involving perhaps one-tenth of the parenchyma, associated obviously with the necrotizing bronchopneumonia. Other organs normal.

Blood Examination.—May 6, 12:05 p. m., death. Blood drawn from heart into oxalate at 1:30 p. m. Blood drawn into a clean bottle (no oxalate) started to clot in forty-five minutes, filmy clots forming on the side of the container. After wiping out with a glass rod more clots formed in one hour. Incomplete coagulation in six hours. After twenty hours the clot was tough and firm, no more forming after this.

Some of this blood (not oxalated) was centrifugalized and this procedure and subsequent handling was associated with acceleration of clotting. The anemia was profound and 50 c.c. of blood after centrifugalization yielded only about 1 c.c. of red cells.

TABLE 7.—Case 5. Coagulation Time of Blood After Death

Plasma H c.c	Plasma D c.c	Calcium Drops	Coagulation Time Minutes	
			Start	End
..	1	5	—	5
1	..	5	15	17
1	1	10	9	—
2	1	15	14	—
3	1	20	11	—

Plasma D was from a normal dog. The coagulation of all mixtures of plasma H was in a fractional manner as described for the whole blood, although very much less marked. (Table 7.) After twenty-four hours the same plasmas were tested with some fresh spleen extract.

TABLE 8.—Case 5. Coagulation Time with Spleen Extract

Plasma H, c.c.	Plasma D, c.c.	Spleen Extract Drops	Calcium Drops	Coagulation Time, Minutes	
				Start	End
1	..	..	5	30	..
..	1	..	5	..	6
1	..	6	5	..	2
..	1	6	5	..	1

Tables 7 and 8 and the observation on the whole blood give conclusive evidence of an excess of antithrombin. There is no lack of prothrombin, as the spleen extract clots the human plasma at once, due simply to a neutralization of the antithrombin, which is the only abnormal factor in the equation.

It is of interest to note the effect of an indirect transfusion which was followed by a febrile reaction and doubled the patient's hemoglobin. The bleeding continued and evidently the antithrombin excess was in no great degree influenced by this procedure. On theoretical grounds it does not seem justifiable to introduce defibrinated blood which is rich in thrombin into a circulation in which antithrombin is in excess. There is every reason to suppose this procedure would be followed by an antithrombin wave which might make matters even worse. The transfusion if attempted should be direct.

LEUKEMA, PURPURA, BLEEDING, ANTITHROMBIN

CASE 6.—Shema. Medical No. 31151. White male, aged 26. Admission July 7. Patient was in a desperate condition due to repeated hemorrhage. Patient had suffered from severe hemorrhages from the nose during the past three weeks. The nasal passages had been packed but the bleeding was not completely checked. Gums had been oozing constantly up till the last day of life. Patient was dyspneic and very weak. There was no history of any previous attacks of hemorrhage, and family history was normal. Patient's past history was negative except for an attack of gonorrhea about five years previously, associated with some joint complications.

Examination.—The patient is very pale and thin. Respirations were of air hunger type. Purpura everywhere over trunk and limbs. The patches were of all sizes from pin-head specks up to spots 1 cm. in diameter, both old and recent. There was edema of feet and ankles. No icterus. The spleen was enlarged. Red blood-cells 1,092,000. W. B. C. 75,300. Hb. less than 10 per cent. Blood smears examined by Dr. Guthrie gave evidence favoring the diagnosis of chronic myelogenous leukemia. There were numerous immature polymorphonuclear leukocytes and myelocytes. Eosinophils were numerous. Nucleated reds very abundant.

Death occurred at 12 m. July 7. No autopsy. Blood aspirated from heart directly into oxalate at 3:30 p. m. Blood also drawn directly into a clean bottle with no oxalate and centrifugalized. During this process a flabby clot formed at 3:50 p. m. This small clot was removed and other secondary clots reformed and were removed at intervals during the next two hours. Small clots formed in this same plasma over night, completing the coagulation, and no subsequent clots reformed after this time. There was no autolysis of the blood clot.

Plasma and serum C from a normal cat. Spleen extract (dilute) from same cat sacrificed at time of experiment. (Table 9.)

TABLE 9.—CASE 6. COAGULATION TIME OF BLOOD AFTER DEATH

Plasma H, c.c.	Plasma C, c.c.	Serum C, c.c.	Spleen Extract Drops	Calcium Drops	Coagulation Time, Minutes	
					Start	End
1	.....	.....	.....	3	17	*25-60+
.....	1	.....	.....	2	4	5
1	1	.....	.....	5	4½	7
2	1	.....	.....	7	6	*8+
3	1	.....	.....	9	7	*10+
1	.....	1	.....	2	3	10
1	.....	.....	15	2	..	3
1	.....	.....	5	2	.....	11
.....	1	.....	.....	2	.....	4
.....	1	.....	5	2	.....	1½
.....	1	1	.....	2	.....	1½
.....	1	.....	15	2	.....	¾

* Coagulation proceeded slowly in fractions after clots were wiped out by glass rod at intervals.

Table 9 shows clearly that the human blood contained an excess of antithrombin and otherwise was normal. The cat serum contained a good deal of thromboplastin and accelerated coagulation of normal as well as human plasma. The human plasma caused definite delay in

coagulation of normal cat's plasma. The fibrinogen was low, but not under 0.1 gm. per 100 c.c.

The two preceding cases furnish evidence that the purpuras and various hemorrhagic symptoms often associated with blood diseases, especially leukemia, are due to an excess of antithrombin. The case of aplastic anemia with inactive bone marrow almost completely excludes the bone marrow as a factor in this antithrombin upset.

It is unfortunate that the platelets were not enumerated in these two cases. It is possible that they were diminished in the first case of aplastic anemia, but very unlikely in the second case (Shema) of chronic leukemia. The platelets are usually increased in number in myelogenous leukemia.

Duke[5] has recently called attention to certain cases of purpura and bleeding in which the platelets are greatly diminished. He believes this to be the sole cause of the tendency to hemorrhage, but it does not seem that this point has been established beyond reasonable doubt, as he has not followed the elements of blood coagulation. The bleeding time in chloroform poisoning may be hours and the coagulation time normal. The platelets are normal or increased, and the essential lesion is a great drop in fibrinogen, rendering the clots too flabby to check hemorrhage.

In the cases reported by him, it is possible that an excess of antithrombin was present. Blood drawn through the tissues (ear puncture) is of no value for the determination of antithrombin (when negative) as the tissue juices may have neutralized all the excess of antithrombin. There may be a sufficient excess of antithrombin to overcome the thromboplastin of the tissues and favor prolonged oozing from cuts and punctures (delayed bleeding time). One can imagine an excess of antithrombin capable of delaying the coagulation of the blood on contact with injured tissues (ear puncture) and so favoring bleeding, yet this excess might be used up by this very contact with the cut tissues, and the blood escaping give a coagulation time of seven to eight minutes. Duke's suggestion that the platelet thrombi normally forming at the ends of the cut vessels are a great aid in stopping hemorrhage is perfectly logical and probably true. There may well be other factors concerned in the diseases which he has studied, and these should be controlled, as the platelet theory is more or less a mechanical explanation.

It is conceivable that the thromboplastic content of various tissues may vary widely under different conditions and may be concerned in promoting or checking hemorrhage when the normal factors of blood coagulation are upset. It is not difficult to imagine a drop in thromboplastin tissue content when there has been a long period of antithrombin excess in the blood, and it is possible that this may be an important

5. Duke, W. W.: The Archives Int. Med., 1912, x, 445.

factor. The methods available at present give unsatisfactory results in attempting estimates of the thromboplastin content of various organs and tissues.

There is a tendency among certain writers to attribute the symptoms of hemorrhagic disease, purpura, bleeding from the mucous membranes, etc., to a temporary increase in fragility or permeability of the capillary vessels. This seems to us to be merely avoiding the issue and ignoring well established facts, which alone are sufficient to explain all the symptoms. It will be admitted that bleeding from the gums, mucous membranes, skin punctures, etc., can be produced experimentally in a variety of ways. We may produce it experimentally by chloroform poisoning, which acts by decreasing the fibrinogen almost to zero in extreme cases, and by peptone injections under favorable conditions where an excess of antithrombin is the essential feature. The bleeding will appear within a few hours after this abnormal condition of the blood appears and vanish as the blood returns toward its normal equilibrium. Surely it is asking much of one's imagination to postulate a variation in fragility of the vessel walls during this short space of time. It will be noted, too, that the bleeding occurs around the teeth where there is a constant inflammation and tissue injury due to trauma and bacteria. The mucous membranes are delicate and subjected to constant trauma which we must imagine cause trivial injuries to the surface and capillaries which are so close to the surface. It will be recalled that purpura is always most marked on surfaces exposed to trauma. It is not too much to suppose that trifling capillary injury is being constantly repaired under normal conditions. Given an abnormality of coagulation, even the most trivial injury may permit of escape of blood into the tissues, or from the surface of the mucous membranes.

MELENA NEONATORUM—PROTHROMBIN ABSENT

CASE 7.—Baby Chapman, age 2 weeks. Birth May 26, 1912. Death June 10, 2 a. m.

Clinical History.—Mother, aged 25, has had two children and one miscarriage. The last child born about a year ago is healthy. Mother gave a positive Wassermann reaction.

May 26. Spontaneous delivery with no difficulty. Placenta normal; no evidence of syphilis. Child measured 47 cm. and weighed 2,800 gm. at birth. The weight of the child diminished as usual and then remained constant with no upward tendency. During the last week weight fluctuated between 2,500 and 2,450 gm. Temperature was normal.

June 4. Retraction of foreskin, which was associated with a good deal of bleeding.

June 5. Continuous oozing from foreskin in spite of all efforts to check bleeding.

June 6. Hemorrhage continued in spite of clamps, various styptics and actual cautery. Human serum, 3 c.c., given subcutaneously. Icterus of the conjunctivae noted.

June 7. No bleeding. Condition much better, given calcium lactate.

June 8. Human serum, 2.5 c.c., given subcutaneously; slight bleeding noted from the cord and little blood in vomitus. No blood in stools.

June 9, 9 p. m. Considerable hemorrhage from the umbilicus, followed by great loss of strength and death June 10 at 2 a. m.

Clinical Diagnosis.—Hemorrhagic disease of new-born; syphilis.

Autopsy June 10, 10 a. m. No. 3735.

Anatomical Diagnosis.—Hemorrhagic disease; absence of blood clots in vascular system; general icterus; subcutaneous and pulmonary hemorrhages; acute splenic tumor; anemia; bronchopneumonia; absence of prothrombin.

Body is that of a well-developed normal appearing negro male infant, 47 cm. in length. The body is cool and rigor mortis is present. Jaundice is well marked in the mucous membranes, conjunctivae and subcutaneous tissues. Thorax opened and blood aspirated from the heart *in situ;* about 30 c.c. of blood obtained. The blood is quite fluid, and there is no evidence of any clot formation in any part of the vascular system. Thorax normal, except for some small areas of purpura in the subcutaneous tissue over the thorax. There are ecchymoses in the thymus and indefinite purplish splotches in the lungs. Thymus is of normal size, very pale, lemon-yellow color and translucent, normal on section.

Heart is of normal size, firmly contracted. The intima and valves throughout are quite normal. Heart muscle is of a pale brownish red color and uniform on section.

Lungs are voluminous and pale lemon color, downy feeling anteriorly, rather heavy and moist posteriorly. The bronchi contain slimy mucus and some vomitus. The mucosa is pale everywhere. The vessels at the hilum are normal and contain no clots. Section shows pale, uniform upper and anterior portion, while the posterior portions show a mottled appearance due to indefinite splotches and specks of bright purple color, looking more like tiny areas of hemorrhage than like areas of consolidation.

Spleen weighs about 6 gm. It is about double the size of the normal spleen of an infant of this size. It is soft; the edges are rounded. The capsule is thin and delicate. Section shows a rather velvety and deep purplish pulp having a chocolate tinge. The Malpighian bodies are small and cleanly outlined. The pulp scrapes off easily and obscures the trabeculae.

Liver is normal size and definitely jaundiced, having an olive-green color with a slight yellowish tint. The lobulation is regular. The cut section is uniform and rather translucent. The gall-bladder contains thin fluid bile and is not particularly distended. No obstruction to the outflow of bile can be made out. Pancreas is of normal size, very pale, milky-white and uniform in appearance.

Mesenteric glands are definitely enlarged and rather conspicuous in the mesentery where the fat has undergone some regression. The lymph-nodes in other parts of the body are rather conspicuous but uniformly pale and translucent on section.

Stomach contains curds and milky fluid. The mucosa is pale. There is no evidence of any hemorrhage. The mucous membrane is intact throughout the intestinal tract wherever examined. The small and large intestine show no evidence of any blood escaping from the mucosa. Intestines are decidedly pale, and except for a certain amount of distention with gas, perfectly normal in gross. Adrenals are rather smaller than normal, about one-half the size of a normal child, but uniform in appearance, with a regular cortex and medulla.

Kidneys are normal. Bladder and prostate are normal. Aorta is perfectly elastic and normal throughout.

Bones: The line of ossification at the lower end of the femur is slightly wider than normal but straight, regular and sharply outlined. The bone-marrow has a currant red and juicy appearance. Brain could not be examined.

Microscopical Notes.—Thymus is normal, not of regressive type. Mononuclear eosinophils are numerous.

Lungs show lesions suggestive of congenital syphilis. The septa are thick and the stroma rich in mononuclear cells. In places are patches of desquamative pneumonia; no fibrin is found in any section. The blood-vessels show thickened walls and the capillaries are relatively inconspicuous in the walls of the alveoli.

Spleen shows normal Malpighian corpuscles. The pulp is full of blood and the sinuses engorged. Phagocytosis by endothelial cells is rare. Nucleated red cells are numerous. Few eosinophils. Mesenteric glands are uniform. Sinuses dilated with endothelial cells, many of which are actively phagocytic, some including as many as six mononuclear cells. Kidney, adrenal and prostate are normal.

The liver cells are normal except for conspicuous bile canaliculi filled with greenish colloid. Between the columns of liver cells are a few nests of mononuclear cells like those seen in congenital syphilis. Levaditi stains in all organs show no spirochetes.

Blood Examination.—Blood taken from right auricle at 10:30 a. m. There were no clots to be found anywhere in the vascular system after the most careful search.

1. Blood containing no oxalate (about 10 c.c.) taken from heart. The corpuscles settled by gravity giving material used in Table 10 (Plasma H, non-oxalated). There was no clotting after a period of forty-eight hours.

2. Blood 20 c.c. added to 2 c.c. sodium oxalate (1 per cent.) and centrifugalized, giving a slightly turbid orange-yellow plasma whose froth was definitely greenish from the presence of bile pigments. The calcium oxalate precipitate was more abundant than usual after centrifugalization. Plasma H — oxalated — used.

3. Spleen Extract H, made by grinding the spleen pulp with sand and two volumes of Ringer's solution followed by filtration.

4. Spleen extract D, fresh extract of same type from dog.

5. Plasma D, and 6, Serum D, both fresh plasma and serum from normal dog.

TABLE 10.—CASE 7.—COAGULATION TIME OF BLOOD AFTER DEATH

Plasma H, Oxalate, c.c.	Plasma H, No Ox. c.c.	Plasma D, c.c.	Serum D c.c.	Calcium Drops	Coagulation Time Minutes
..	1	..	1	..	9
..	1	..	2	..	9
..	..	1	..	5	7
1	..	..	..	5	*
1	..	1	..	7	3
2	..	1	..	12	4
2	..	1	..	12	4
..	..	1	†	10	5

* = No clot in forty-eight hours. † = 1 c.c. Ringer's solution.

1. Dog plasma (1 c.c.) + spleen extract H, 7 drops + calcium, 5 drops = clot in 1½ minutes.

2. Plasma H., no oxalate (1 c.c.) + spleen extract H, 9 drops = no clot in 24 hours; at this time clotted by adding serum D.

3. Plasma H., oxalated (1 c.c.) + spleen extract D, 5 drops = no clot in 24 hours; then clotted by serum D.

4. Plasma H., oxalated (1 c.c.) + spleen extract D, 4 drops = no clot in 24 hours; then clotted by serum D.

5. Plasma H., oxalated (1 c.c.) + serum D (1 c.c.) = clot formed in 12 minutes.

6. Plasma H., oxalated (1 c.c.) + pure thrombin, 7 drops = clot; starts in 6 minutes; complete in 10 minutes.

7. Plasma H., no oxalate (½ c.c.) + pure thrombin, 7 drops = firm clot in 13 minutes.

The data above make it absolutely certain that in this case of melena neonatorum the only abnormality was the absence of *prothrombin*. The plasma is readily clotted by fresh serum or pure thrombin which later was obtained through the kindness of Dr. Howell and prepared after his method described in a recent publication. This plasma does not delay the coagulation of normal plasma showing an absence of any antithrombin excess. Fibrinogen and calcium are present at least in normal amounts. The spleen extract from this case contains an abundance of thromboplastin. There is clinical evidence of improvement following treatment by human serum which, of course, furnishes the missing factor of coagulation, but in this case the improvement was transient.

We have reported a similar case in an earlier communication, in which the evidence pointed pretty conclusively to a total absence of prothrombin. This case strengthens the argument that this group of cases is quite clean cut with constant blood-findings. There was conclusive proof of fibrin formation in the lung of this case previously reported, but this coagulum had been formed several days previous to the onset of hemorrhagic tendencies and death. Also this first case gave no evidence of any organic or infectious disease and no hint of the source of prothrombin formation.

The case reported here shows evidence of the syphilitic virus although no spirochetes can be demonstrated and the placenta was normal. It is possible that syphilis was important in the etiology of this case, but study of the organs gives no clue to the origin of prothrombin.

CONCLUSIONS

The antithrombin-prothrombin balance in the blood is in delicate equilibrium but under normal conditions there are strong factors which can preserve this balance. Under experimental conditions this may necessitate rapid neutralization of antithrombin excess; again a rapid production of fresh antithrombin or prothrombin. There are wide margins of safety in the normal animal.

This antithrombin-prothrombin balance may be temporarily or permanently upset under disease conditions as reported in the preceding cases. The *prothrombin* factor is rarely involved, but it may drop to zero (Case 7) or to a low level (Case 1) which will be associated with hemorrhagic symptoms.

The *antithrombin* factor is frequently involved and if this element is much increased above normal there will be a tendency toward hemorrhage, purpura, etc., depending in part on the duration of the change, but especially on the amount of antithrombin excess.

It may be assumed that during these wide fluctuations of *antithrombin* it may fall *below* normal, whereupon there would be a tendency to vascular thrombosis. Given a low antithrombin content a minor injury to the intima might initiate a thrombus which would grow rapidly. With the growth of a thrombus there would be the formation of much thrombin which would escape into the blood and stimulate the organ (liver) producing antithrombin. This might result in an antithrombin wave—a period of antithrombin excess (Case 4)—which would check the growth of thrombi and give the endothelium opportunity to cover over the fresh thrombi, thus removing the foci of thrombin formation. The antithrombin wave may fall promptly to normal or persist for weeks, but if its duration is a matter of days there will appear signs of hemorrhagic disease (Case 2).

It seems highly probable that under certain conditions liver injury or disease may be associated with an excess of antithrombin in the blood capable of giving hemorrhagic symptoms (Cases 1 and 2). Also certain substances in the blood (peotone, thrombin) will bring about an overproduction of antithrombin due probably in great part to stimulation of the liver. Under this heading may be grouped cases of septicemia (reported previously), pneumonia (Dochez) endocarditis, miliary tuberculosis (Case 3) generalized vascular thrombosis (Case 4), etc.

True hemorrhagic disease is rarely associated with simple obstructive icterus, contrary to common belief. Delayed coagulation time in jaundice may be influenced favorably by calcium, but such cases do not suffer from bleeding unless there is some other abnormality—for example, an excess of antithrombin. In these rare cases of true hemorrhagic disease associated with profound icterus, we may presuppose some liver disease and an upset in the antithrombin-prothrombin balance (Case 1). Calcium has no effect on this condition.

Disease of the blood-forming organs may present symptoms of hemorrhagic disease (aplastic anemia, Case 5 and leukemia, Case 6) because of an excess of antithrombin in the blood. It is unlikely that the blood-forming tissues are directly concerned in the antithrombin production as this element is much in excess in the case of anemia (Case 5) with complete marrow aplasia. It is possible that the products of blood-cell disintegration may stimulate an overproduction of antithrombin. It will be recalled that purpura and hemorrhagic tendencies are more common in acute leukemias in which the evidences of blood-cell disintegration are most marked. It is probable that the majority of hemorrhagic

cases and purpuras associated with leukemias and anemias belong in the antithrombin group.

The disease called *melena neonatorum* in many, perhaps all, instances is characterized by a relatively sudden disappearance of prothrombin from the blood. This condition usually develops during the first two weeks of life and is often fatal. The cases react favorably to fresh serum treatment.

Treatment of hemorrhagic disease should follow a careful analysis of the blood as harm can be done by faulty treatment. In cases of low or absent prothrombin, it is clear that serum which is rich in this element is indicated and in many cases produces almost miraculous cures. It should be given intravenously if possible. Direct transfusion is of even greater value.

Treatment of antithrombin cases offers great difficulties. Serum treatment offers no help and it may even stimulate a still greater overproduction of antithrombin. Indirect transfusion is open to the same criticism (Case 5) as large amounts of thrombin are introduced. It may be possible to find some safe way to introduce thromboplastin into the blood-stream in the hopes of neutralizing the antithrombin excess. If the means by which the antithrombin is neutralized or used up in the normal body can be found out by various animal experiments, the solution of this problem in treatment of antithrombin cases may be reached. At present direct transfusion seems to offer the greatest hope of permanent benefit.

PRACTICAL STUDIES ON THE SO-CALLED SYPHILIS "ANTIGENS," WITH SPECIAL REFERENCE TO CHOLESTERINIZED EXTRACTS *

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Of most interest and importance in the serum diagnosis of syphilis is the question of "antigens," not only from the standpoint of efficiency and specificity, but also from the possibility of throwing more light on the nature of the reaction.

When Wassermann, Neisser and Bruck originally applied the Bordet-Gengou phenomenon of complement-fixation to the diagnosis of syphilis, the causative organism, *Treponema pallidum,* had not been isolated in pure culture, so they selected the fetal liver of congenital syphilis because rich in the *Treponema,* for making the antigen. Securing well-marked and definite results, they concluded that the specific antigenic properties of the extract were due to the presence of the *T. pallida* and that the reaction was an example of specific union of antigen and antibody. Subsequent investigation indicates that this is partially true, as the antigenic principles of *T. pallida* are extractable in salt solution, and in some cases of syphilis there exists a true antibody which will unite with the true *T. pallida* antigen. But it is probable that if the original investigators had had a pure culture of *T. pallida* for antigen the great practical value of the syphilis reaction would not have been readily realized, as recent work with *T. pallida* antigens shows weaker and more inconstant results and is of less practical value as compared with tissue extracts.

The belief in the specific nature of the "antigen" was early shaken by the investigation of Marie and Levaditi,[1] who showed that an extract of a normal liver could replace an extract of a syphilitic liver in the reaction. This discovery was abundantly confirmed by the subsequent investigations of Porges and Meier,[2] Landsteiner, Müller and Potzl,[3] Levaditi and Yamanouchi,[4] Noguchi and Bronfenbrenner,[5, 6] and others,

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1. Marie, A., and Levaditi, C.: Ann. de l'Inst. Pasteur, 1907, xxi, 138.
2. Porges, O., and Meier, G.: Berl. klin. Wchnschr., 1908, p. 731.
3. Landsteiner, K., Müller, R., and Potzl, O.: Wien. klin. Wchnschr., 1907, p. 1565.
4. Levaditi, C., and Yamanouchi, T.: Compt. rend. Soc. de biol., 1907, lxiii, 740.
5. Noguchi, H.: Jour. Exper. Med., 1909, xi, 84.
6. Noguchi, H., and Bronfenbrenner, I.: Jour. Exper. Med., 1911, xiii, 43.

with various extracts of various non-syphilitic organs. These investigations also showed that the "antigen" was soluble in alcohol and probably of the nature of a lipoid. Hence the original conceptions of the reaction were not tenable, although it is fortunate that a tissue was selected for the original "antigen"; otherwise this reaction, of great diagnostic value and therapeutic guidance, may have been delayed in its development.

As soon as the important rôle of lipoids in this reaction was demonstrated, attempts were made to substitute the complicated tissue extracts with pure solutions of lipoids. Among these, lecithin, sodium taurocholate, glycocholate, oleic acid, oleates, cholesterin, etc., have been tried alone and in combination. It was soon found that many tissue extracts were unsuitable for the reaction because of the presence of impurities which caused non-specific inhibition of hemolysis or were in themselves hemolytic. Noguchi, and later Noguchi and Bronfenbrenner, endeavored to purify extracts by fractional solution and precipitation and succeeded in devising an extract of acetone insoluble lipoids composed largely of lecithin which has given good results. Later, Browning, Cruickshank and Mackenzie[7] found that a mixture of lecithin and cholesterin yielded particularly specific reactions in syphilis. The latest notable advance has been the suggestion of Hans Sacks[8] to combine the alcoholic extracts of normal organs with cholesterin. He has found such preparations to possess properties equal to the best syphilitic extracts. This work has been confirmed by McIntosh and Fildes,[9] who feel that in this combination the requirements of a "standard antigen" have finally been realized. We have studied these antigens with particular care, the results being given in this communication.

It was hoped that with the isolation of the *Treponema pallidum* the question of specific antigen would be solved. Noguchi[10] having accomplished the difficult task of isolation, prepared an antigen by extracting several strains in salt solution and used the antigen in the serum diagnosis of syphilis with the result that a specific antibody was demonstrated, especially in tertiary syphilis, or cases under treatment. Noguchi considered that reactions with specific *T. pallida* antigen would indicate the degree of resistance of the patient as shown by the amount of complement fixed, depending on the quantity of specific antibody present in the patient's serum. The work as continued by Craig and

7. Browning, C. H., Cruickskank, J., and Mackenzie, J.: Biochem. Ztschr., 1910, xxv, 85; Jour. Path. and Bact., 1910, xiv, 484.

8. Sacks, H.: Berl. klin. Wchnschr., 1911, p. 2066.

9. McIntosh, J., and Fildes, P.: Ztschr. f. Chemotherapie, 1912, i, 79.

10. Noguchi, H.: Jour. Am. Med. Assn., 1912, lviii, 1163.

Nickols[11] and ourselves,[12] shows that reactions with *T. pallida* antigens are generally weaker and more inconstant than reactions with tissue extracts and are of limited value. Craig and Nickols also showed that fixation would occur with antigens of *S. pertenius* (yaws) and *S. microdentium*. This indicates a group reaction, and when these results are compared to similar studies of others and our own on the differentiation of streptococci, diphtheria bacilli and the typhoid-colon group of bacilli by specific complement fixation reactions, it is evident that either the amboceptor produced by a member of the group is not specific for its antigen or that by our present methods we are unable to extract the definite and specific antigenic substance from the organism.

The sum total of investigation indicates, therefore, the presence of two antisubstances in the serum of a syphilitic patient. One is of the nature of a reactionary substance of the body cells, a product of decomposition or an altered body protein ("reagin"), which has as its chief property an affinity for lipoids. This substance is regularly produced by the *Treponema pallidum* and is responsible for the positive complement "fixation" with lipoidal extracts. A similar "reagin" is produced during infections with the spirochete of yaws and the bacillus of leprosy and is responsible for the positive Wassermann reaction found in these diseases. Our work with spirochete antigens indicates also that this "reagin" will yield non-specific reactions of minor degree with the lipoidal substances present in culture media and other alien organisms, as *B. typhosus* and *B. cholera*. The true nature of this "antibody," so well designated by Simon as "lipodophilic," is unknown, although the work of Klausner, Noguchi, Friedmann and others, tend to show that it is of the nature of a globulin.

The second antisubstance is probably the true pallida antibody in the nature of an amboceptor, although as far as has been demonstrated by complement fixation reactions, its presence in syphilitic serums is inconstant, and, as already mentioned, it reacts with a group of spirochetes closely resembling the *Treponema pallidum*.

However, since a lipodophilic "reagin" seems to be such an important and prominent factor in the serum diagnosis of syphilis, because of its affinity for lipoids, it may be that considerable light may be thrown on the specificity and nature of Wassermann's reaction by a closer study of lipoids. As will be shown in this communication, there can be little doubt of the importance of cholesterin in this connection and it is not beyond the realm of possibilities that a particular lipoid altered by syphilitic infection, may solve the problem of "specificity."

11. Craig, C. F., and Nickols, H. J.: Jour. Exper. Med., 1912, xvi, 336.
12. Kolmer, J. A., Williams, W. W., and Laubaugh, E. E.: Jour. Med. Research, July, 1913.

ANTIGEN

From the practical standpoint any extract or preparation to be suitable as "antigen" should answer the following requirements:

1. It should possess a high degree of sensitiveness and specificity for syphilitic serum.
2. It should not give false reactions with normal serums, a proper technic being used.
3. It should be reasonably stable and not difficult of preparation, and different preparations should bear a reasonable relationship to each other in their properties.

The large number of different extracts and combination preparations of the lipoids advocated from time to time bear definite witness to the unsatisfactory state of our knowledge and is largely responsible for the inconstant and varying results of different workers, and demonstrates the need of a "standard antigen."

We have made an extensive comparative study of the usual and better known "antigens," and the object of the present communication is to briefly record our results from a practical standpoint, along with a technic which we are using and which in our experience renders the reaction more reliable and less apt to yield pseudo-reactions, namely, to use several "antigens" with each serum being tested, for results show quite definitely that the lipodophilic reagin or the so-called syphilis "antibody" in different serums has a different affinity for different lipoidal extracts, and that these differences are independent of any changes occurring in the "antigens" themselves. With the serum of active syphilis most any extract will serve to yield a positive reaction, but when the amount of "reagin" is small, as in long-standing or vigorously treated cases, the question of "antigen" and technic becomes one of considerable importance. It is in such cases that we have noted the varying degrees of reaction with different "antigens" of equal efficiency, and it was not uncommon to find a negative reaction with one antigen and positive with the others. In not a few cases dependence on a single extract would have led to false negative reaction with serums of cases where the treatment was being guided by the serum reactions.

METHOD OF STUDY

Since alcoholic extract of syphilitic liver is the most widely used "antigen," we have compared the properties of other "antigens" to several such extracts which we have used for over two years, and are of proven value. The method of comparative study consisted, therefore, in using from three to ten different extracts with each serum and comparing results. As will be pointed out later, all extracts were titrated before using and only those included in the study as proved satisfactory.

The antisheep hemolytic system was used, complement and amboceptor being titrated before tests were set up, and one unit employed. There is such a close quantitative relationship between complement and amboceptor that they must be accurately adjusted to avoid the influence of natural antisheep amboceptor in human serums. The serums were always inactivated by heating to 55 C. for one-half hour and used in doses of 0.1 to 0.2 c.c. Serum, antigen, amboceptor, complement, corpuscle and hemolytic controls were set up each time as is our routine practice. Serum, antigen and complement are incubated one hour; amboceptor and corpuscles added and reincubated for one to two hours, depending on the rapidity of hemolysis in the controls, and then placed over night in the refrigerator at a low temperature, readings being made the following morning.

"ANTIGENS" STUDIED

The following extracts were studied and may be divided as follows:

I. Extracts of syphilitic liver:
   a. Four alcoholic extracts.
   b. Two acetone extracts (Kolle and Stiner).

II. Extracts of normal organs:
   a. Alcoholic extracts.
      1. Of normal liver.
      2. Of beef heart.
      3. Of guinea-pig heart.
   b. Acetone extracts.
      1. Of normal liver.
   c. Two extracts of acetone-insoluble lipoids (Noguchi).

III. Cholesterinized alcoholic extracts:
   a. Extracts of normal organs (Sacks).
      1. Of beef heart.
      2. Of human heart.
      3. Of guinea-pig heart.
      4. Of normal liver.
      5. Of acetone-insoluble lipoids.
   b. Extracts of syphilitic liver.
      1. Alcoholic extracts.
      2. Acetone extracts.

All antigens were titrated for antigenic, anticomplementary and hemolytic doses. The serum of a secondary case of syphilis is used in amount of 0.1 c.c. with ascending doses of antigen, and that dose of antigen just giving complete inhibition of hemolysis recorded as the antigenic dose. In using this antigen, at least two or three times this antigenic dose is employed because the one unit may be insufficient with other serums. The anticomplementary dose must be at least eight to ten times the antigenic unit before the extract is accepted as satisfactory. This margin of safety we consider advisable, especially with the cholesterinized extracts. This rule was followed with all "antigens" so as to secure uniform comparison of the various extracts.

PREPARATION OF "ANTIGEN"

1. Alcoholic Extracts of Syphilitic Liver.—These were prepared of the liver of syphilitic fetuses in which the *Treponema pallidum* was found. Fatty livers were avoided and those of stillborn fetuses are to be preferred. Not infrequently a fetus is secured with many or all of the usual signs of luetic infection and the mother yield a positive Wassermann reaction and yet one fails to find the *Treponema pallidum* by dark field illumination. Under these circumstances we frequently prepare an antigen but discard it unless it shows a high antigenic value and is free of anticomplementary and hemolytic effects to a safe degree. We have also used an imported German alcoholic extract of syphilitic liver, but have not as yet found these extracts superior to a satisfactory preparation of our own. These extracts are prepared as follows:

A portion of liver is weighed, minced, ground with quartz sand and treated with 10 volumes of ninety-six per cent. alcohol. The mixture is shaken mechanically with glass beads for twenty-four hours and extracted in the incubator for ten days; filtered, measured and loss of evaporation made up. This alcoholic extract is then diluted 1:10 with saline solution and titrated for antigenic, anticomplementary and hemolytic doses. If a shaking apparatus is not available extraction in the incubator should be continued for two weeks.

2. Acetone Extracts of Syphilitic Liver.—Such extracts have been claimed by Kolle and Stiner[13] to be more sensitive than alcoholic extracts especially with serums from cases of syphilitic infection of the nervous system. These are prepared as follows:

Two grams of dried syphilitic liver are ground with sand and treated with 60 c.c. of chemically pure acetone, incubated over night, shaken mechanically with glass beads for twenty-four hours, placed at room temperature for forty-eight hours, filtered and titrated.

3. Alcoholic Extract of Normal Organs.—These were prepared of the muscular portions of beef heart, guinea-pig heart and of a normal liver containing but a small amount of fat, in exactly the same manner as alcoholic extracts of syphilitic liver except that extraction in the incubator is continued two weeks.

4. Acetone Extract of Normal Liver.—This was prepared in the same manner as acetone extract of syphilitic liver.

5. Acetone-Insoluble Lipoid Extract (Noguchi).—The preparation of this antigen is so well known that it is only for completeness that the technic of preparation is here included.

A mashed paste of muscle of ox-heart is extracted with ten parts of absolute alcohol at 37 C. for four days. It is then filtered through paper and the filtrate collected and brought to dryness by evaporation. The electric fan is not necessary for the filtrate will evaporate in twelve to twenty-four hours if poured into large flat dishes. The residue is then taken up with a sufficient quantity of ether and the turbid ethereal solution is allowed to stand for a few hours in a cool place until cleared. The clear ethereal portion is then carefully decanted into another clean beaker and condensed into a small quantity by evaporating a portion of the ether. The concentrated ethereal solution is now treated with 10 volumes of pure acetone. A light yellow precipitate forms which is allowed to settle and the supernatant fluid decanted off. Dissolve each 0.3 gm. of this substance in 1. c.c. of ether and add 9 c.c. of pure methyl alcohol. It is usual to find that the greater part of the substance goes into solution. This alcoholic solution remains unaltered for a long time and is kept as stock, from which the emulsion for immediate use may be prepared at any time by mixing 1 c.c. with 9 c.c. of saline solution. This solution is then titrated for antigenic, anticomplementary and hemolytic action. It may be necessary to prepare several

13. Kolle, W., and Stiner, O.: Deutsch. med. Wchnschr., 1911, xxxvii, 1739.

such extracts before one is found thoroughly satisfactory. The ox-heart preparations were uniformly more satisfactory than those of the liver. The main drawback of this antigen is the expense of preparation, and many extracts prove unsatisfactory. For this work we have used three extracts of proved value.

6. Cholesterinized Alcoholic Extract of Normal Organs.—These were prepared in the same manner as the plain alcoholic extracts with the addition of 0.4 per cent. of Kahlbaum's cholesterin, or 0.4 gm. per each 100 c.c. of the filtrate, this amount having been found by Swift most satisfactory. All of this cholesterin does not usually go into solution and it may be necessary to refilter after vigorous shaking and standing over night. The extracts of human and beef heart have been better in our hands than the extracts of guinea-pig heart, insofar that the latter extract may be too highly anticomplementary. We have attributed this to the presence of fat and the extraction of undesirable derivatives. It is advisable, therefore, to use only the muscular portions. As will be pointed out later, these extracts possess such high antigenic value that they must frequently be highly diluted to appreciate their sensitiveness.

7. Cholesterinized Extract of Acetone-Insoluble Lipoids in Methyl Alcohol.—This was prepared by adding 0.4 per cent. cholesterin to a suitable extract of acetone-insoluble lipoids in pure methyl alcohol. Since the plain alcohol soluble acetone-insoluble fraction is composed largely of lecithin, the extract now becomes essentially a mixture of lecithin and cholesterin.

8. Cholesterinized Extract of Syphilitic Liver.—Two alcoholic and one acetone extracts of syphilitic liver were prepared according to the methods already given and cholesterinized by adding 0.4 per cent. of pure cholesterin.

COMPARISON OF ANTIGEN PROPERTIES

I. Extracts of Syphilitic Liver:

(a) Alcoholic Extracts of Syphilitic Liver: These extracts are probably more widely used than any other and are regarded by many in higher favor than extracts of normal organs, because of the possibility of their containing products of *T. pallidum* itself. On the other hand, there is little doubt that precedent has considerable influence and the impressions of the original explanation of the reaction is largely responsible for a certain hesitancy in depending on other extracts. One fact should be borne clearly in mind, however; that one good extract of a normal organ is better than a number of poor extracts of syphilitic liver or of liver supposedly syphilitic. We have used several good extracts throughout the study, and, as before stated, results are recorded in comparison to these. Occasionally we have used an imported German extract of syphilitic liver for comparison with our extracts, but the results were entirely similar to those obtained with our own preparations.

While in general it is a difficult matter to express percentages of positive reactions in the later stages of syphilis because of the difficulty of obtaining a reliable history or of indefinite symptoms, we have found our alcoholic extracts of syphilitic liver to yield 87.2 per cent. positive reactions in the primary stage; 96.7 per cent. in the secondary and about 90 per cent. in the tertiary stages, a large proportion of our tertiary cases being infections of the nervous system. With cholesterinized extracts

the percentage of positive reactions in the tertiary and latent stages, or after vigorous treatment, is considerably higher.

(b) Acetone Extracts of Syphilitic Liver: Two extracts were prepared and used with alcoholic extracts of syphilitic liver in testing 443 serums and forty-two cerebrospinal fluids. Of this number of tests, 227 yielded positive reactions.

1. In 68.7 per cent. of cases the acetone extracts yielded results equal to those obtained with the alcoholic extracts.

2. In 4.4 per cent. the acetone extracts yielded stronger or better marked reactions.

3. In 18.9 per cent. of cases the reactions with the acetone extracts were weaker than those with the alcoholic extracts.

4. In 15 or 6.6 per cent. of reactions the acetone extracts yielded negative reactions with the following cases, whereas the reactions were positive with the alcoholic extracts. The cases were as follows:

Two cases of primary syphilis.
Two cases of paresis.
One case of tabes dorsalis.
Three cases of hemiplegia with positive histories.
Five cases of tertiary syphilis with gumma formation.
One case with leg ulcers and positive history.
One case of hereditary syphilis.

5. In the following three, or 1.3 per cent. of cases, the acetone extracts yielded positive reactions, whereas these were negative with the alcoholic extracts:

One case of paresis.
Two cases of tertiary syphilis with positive histories.

It will be noted that acetone extracts of syphilitic liver have not been found superior to alcoholic extracts, and in about 25 per cent. of cases yielded reactions which were weaker than those with alcoholic extracts, or clearly negative. In reference to pseudo-reactions with serums of patients with high temperature, lead poisoning, etc., the results were comparable to the alcoholic extracts in every particular. When suitably preserved, these antigens have been found quite stable.

II. Extracts of Normal Organs:

(a) Alcoholic Extract of Normal Liver: One such extract was used, although several were made but discarded, because too highly anticomplementary and too low in antigenic value. This extract was used in testing 140 serums and seven cerebrospinal fluids along with the alcoholic extracts of syphilitic liver. Of these specimens, fifty-six yielded positive results.

1. In 73.2 per cent. of cases the reactions with this extract of normal liver yielded a similar reaction to those with the extracts of syphilitic liver.

2. In no instance did this extract yield a stronger reaction.

3. In 23.2 per cent. of cases the extract gave weaker reactions.

4. In 3.5 per cent. of cases this extract yielded false negative reactions.

As will be noted, there can be little doubt that the extract of normal liver was less efficient than the extract of syphilitic liver. When this extract was cholesterinized its antigenic properties were doubled and in results it was equal to, and in some case proved superior to the alcoholic extracts of syphilitic liver. When compared to results obtained with extracts of beef and guinea-pig heart, it will be noted that the liver is least suitable for the preparation of extracts of normal organs.

(b) Alcoholic Extracts of Guinea-pig and Beef Heart: These extracts enjoy considerable favor with many workers and are probably the organs best adapted for preparing alcoholic extracts of normal organs, because the anticomplementary effects are likely to be low and the antigenic value sufficiently high as to render them serviceable. In our experience, extract of human and beef heart are more satisfactory, because pig-heart extracts are not infrequently highly anticomplementary, a fact which may be attributed to the presence of fat and extraction of undesirable derivatives. As will be seen later, when these same extracts are cholesterinized, the antigenic value is so highly increased as to render them even more delicate than the extracts of syphilitic liver.

Plain alcoholic extracts of pig and beef heart were used in testing 129 serums and ten cerebrospinal fluids, along with the usual extracts of syphilitic liver. Positive reactions were secured with fifty-two of these specimens. Suitable extracts of pig and beef heart are closely similar in antigenic properties.

1. In 71.1 per cent. of cases the reactions were equal to those obtained with the "antigen" of syphilitic liver.

2. In 1.9 per cent. of cases the reactions were stronger.

3. In 13.4 per cent. the reactions were weaker.

4. In the following three cases these extracts gave positive reactions, whereas with the alcoholic extracts of syphilitic liver the results were negative:

One case of lead poisoning with a positive history of lues.
One case of tabes dorsalis.
One case of tertiary syphilis with positive history.

5. In the following four cases these extracts yielded negative reactions with positive results with the alcoholic extract of syphilitic liver:

One case of hemiplegia, history positive.
One case of paresis.
One case of hereditary syphilis.
One case of Jacksonian epilepsy. History and autopsy not obtainable.

(c) Acetone Extract of Normal Liver: One suitable extract was used along with acetone and alcoholic extracts of syphilitic liver in testing twenty-four serums. The results were similar to those of the acetone extracts of syphilitic liver (already given), except that in 12.5 per cent. of cases the reactions were weaker.

(d) Acetone-Insoluble Lipoids (Noguchi): Three satisfactory extracts along with alcoholic extracts of syphilitic liver were used in testing 315 serums and forty-five cerebrospinal fluids, with the following results:

1. In 73.0 per cent. of cases the results were equal.
2. In 10.8 per cent. the reactions were stronger.
3. In 9.7 per cent. the reactions were weaker.
4. In the following five, or 3.2 per cent. of cases, the reactions were positive, whereas with the alcoholic extracts of syphilitic liver the results were negative:

One case of paresis.
One case of tabes dorsalis.
Three cases of secondary syphilis.

5. In the following three, or 1.8 per cent., of cases the reactions were negative, whereas with the alcoholic extracts of syphilitic liver positive reactions were secured:

One case of hereditary syphilis.
One case of paresis.
One case of maternal syphilis.

It must be remembered in this connection that all serums were used inactivated and with an antisheep hemolytic system. Therefore, these were not conducted by the method of Noguchi. We consider a satisfactory extract of acetone-insoluble lipoids as ranking next in efficiency to cholesterinized alcoholic extracts among the "antigens" prepared of normal tissues.

III. Cholesterinized Alcoholic Extracts:

The addition of cholesterin to extracts of normal and syphilitic organs increases the antigenic properties of the "antigen" to a marked degree. The use of such extracts renders the Wassermann reaction even more sensitive, so much so that careful investigation is necessary for ascertaining the probability of false reactions with normal serums. We have found this to occur in a certain proportion of cases, and therefore these extracts, while marking a distinct advance in this field, must be used with care and caution.

The method of preparing these extracts is very simple and has already been given. The addition of 0.4 gm. of pure cholesterin to each 100 c.c. of a filtered alcoholic extract of an organ, preferably human, pig or beef heart. Fat should be avoided.

In this manner we have prepared and studied cholesterinized alcoholic extracts of beef, human and pig heart and human liver. An extract of acetone-insoluble lipoids was cholesterinized and compared to a plain extract; also alcoholic and an acetone extract of syphilitic liver were cholesterinized and compared to plain extracts.

(a) Influence of Cholesterin on Antigen Properties of Extracts: The influence of cholesterin on the antigenic and anticomplementary properties of the extracts was then studied by titration, plain extracts being tested at the same time and in the same manner.

Method.—The antigenic titration consisted briefly in diluting the extracts with normal saline solution and placing increasing doses in a series of six test-tubes as follows: 0.01 c.c., 0.05 c.c., 0.1 c.c., 0.2 c.c., 0.25 cc., and 0.3 c.c. One unit of complement and 0.1 c.c. of inactivated serum from a case of secondary syphilis were added to each tube and tubes incubated for an hour, when 1. c.c. of sheep corpuscles and one unit of amboceptor were added. Tubes are reincubated for one to two hours and then placed in the refrigerator over night. Readings are made and recorded according to the amount of inhibition of hemolysis as indicated by the signs, ++++ (100 per cent. inhibition); +++ (75 per cent. inhibition); ++ (50 per cent. inhibition); + (25 per cent. inhibition); ± (less than 25 per cent. inhibition); — (completely hemolyzed). That dose of antigen giving complete or 100 per cent. inhibition of hemolysis is recorded as the antigenic unit. In conducting Wassermann reactions at least two or three times this dose is used, provided that this amount is no more than one-fourth the anticomplementary dose. One may also estimate the antigenic value by determining the number of units of complement "fixed." The anticomplementary titration is conducted in a similar manner by adding 0.1 c.c., 0.2 c.c., 0.4 c.c., 0.8 c.c., 1.0 c.c., and 2.0 c.c. of the diluted "antigen" to a series of tubes, adding a unit of complement and sufficient salt solution. We prefer to incubate these tubes one hour along with the antigenic titration so that the complement is subject to the same deterioration in the incubator. At the end of an hour a unit of amboceptor and corpuscles are added and tubes returned to the incubator for one to two hours, after which readings may be made at once, or after tubes have been placed in the refrigerator over night. That dose of "antigen" just beginning to inhibit hemolysis is recorded as the anticomplementary dose. As is customary, serum, complement, amboceptor and corpuscle controls are set up.

In Table 1 are given some of the results of such titrations of cholesterinized and plain extracts made from time to time for comparison.

The addition of 0.4 per cent. of cholesterin, therefore, increases the antigenic value of an extract at least two to four-fold and does not usually alter the anticomplementary dose. It will also be noted that 0.4 per cent. cholesterin in absolute alcohol, the same proportions as are used in cholesterinizing the extracts, has an antigenic value which may be estimated at about three to six times weaker than cholesterinized tissue extracts. We have not found cholesterinized extracts more stable than plain extracts,

and they must therefore be guarded by frequent titrations and controls against anticomplementary action.

(b) Cholesterinized Extracts and Normal Serums: After using several cholesterinized, along with a number of plain extracts in conducting Wassermann reactions, we soon found that with a number of serums inhibition of hemolysis occurred only with cholesterinized extracts. In the larger number of these instances there was either a history of lues or the clinical condition was such as strongly to indicate this infection. But in other serums where these extracts gave a small amount of inhibi-

TABLE 1.—ANTIGENIC AND ANTICOMPLEMENTARY VALUES OF PLAIN AND CHOLESTERINIZED EXTRACTS

Extracts	Plain Extracts		Same Extracts Cholesterinized	
	Antigenic Unit, c.c.	Anticomplementary Unit, c.c.	Antigenic Unit, c.c.	Anticomplementary Unit, c.c.
Alcoholic, of syphilitic liver, diluted 1:10, No. 1.....	0.1	1.0	0.05	1.0
Alcoholic, of syphilitic liver, diluted 1:10, No. 2.....	0.2	2.0	0.1	1.5
Acetone, of syphilitic liver, diluted 1:10	0.2	0.8	0.1	0.8
Alcoholic, of normal liver, diluted 1:10	0.2	2.0	0.1	2.0
Acetone-insoluble lipoids, diluted 1:20	0.2	1.0	0.15	1.0
Alcoholic, beef heart, diluted 1:10	0.1	2.0	0.05	2.0
Alcoholic, human heart, diluted 1:25	0.1	2.5	0.05	2.5
Alcoholic, pig heart, diluted 1:10	0.1	2.5	0.025	2.5
0.4 per cent. cholesterin in absolute alcohol diluted 1:10	...	...	0.3	1.0

tion the history and clinical condition indicated with a fair degree of accuracy the absence of lues. Since, however, it is a very difficult matter definitely to exclude syphilis in the average hospital case we have tested our own blood and the blood of others, mostly physicians, in whom the possibility of syphilitic infection is definitely ruled out. Twenty such serums were tested as follows: The cholesterinized extracts were used in double the antigenic dose; the serums were inactivated and used in amounts of 0.1 c.c., 0.2 c.c., 0.3 c.c. and 0.4 c.c. The balance of the method was exactly the same as in our routine Wassermann reaction; one titrated unit of amboceptor being used. The results were best marked

with the 0.1 and 0.2 c.c. of serum because the larger doses introduced sufficient natural antisheep amboceptor to cause undue hemolysis. The results of the experiment, therefore, are those found with the 0.2 c.c. dose of serums (Table 2).

It will be noted that the cholesterinized extract of beef heart gave twenty-five or less per cent. inhibition of hemolysis with half of the serums tested, and this extract was certainly not anticomplementary in the dose employed. The remaining extracts yielded pseudo-reactions of about 10 per cent. inhibition of hemolysis with 5 to 10 per cent. normal serums. The sensitiveness of these extracts is also noted in the higher proportion of positive reaction with normal rabbit serum.[14] When using these extracts in amounts of half the anticomplementary dose the per-

TABLE 2.—CHOLESTERINIZED EXTRACTS WITH NORMAL SERUMS

Extracts	Dose Used, c.c.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Cholest. beef heart (1:10).....	0.1	+	—	+	±	—	—	—	±	+	—	—	±	±	±	±	—	..	—	—	+
Cholest. human heart (1:25)...	0.1	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cholest. pig heart (1:10).....	0.1	±	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	—
Cholest. normal liver (1:10)..	0.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	±
Cholest. alcoholic extract syphilitic liver (1:10)	0.1	±	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	±
Cholest. acetone extract syphilitic liver (1:10).....	0.2	±	—	—	—	—	—	—	—	—	—	—	—	—	±	—	—	+	—	—	—
Cholest. acetone insol. lipoids (1:10)	0.2	—	—	—	—	—	—	—	—	±	—	—	—	—	—	—	—	+	—	—	—
Plain alcoholic extract syphilitic liver (control)	0.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Serum control	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

+ = 25 per cent. inhibition. ± = less than 25 per cent. inhibition.
— = complete hemolysis.

centage of pseudo-reactions is increased. As will be shown later, not a few cases of tertiary lues or cases actively treated with salvarsan and mercury, the quantity of syphilis "reagin" in the serum being small, yielded negative reactions with plain extracts and only 25 per cent. inhibition of hemolysis with the cholesterinized extracts, rendering it difficult to express an opinion in cases more worthy of delicate reactions than those in which the clinical diagnosis is quite evident. We have noted that the syphilis "reagin" apparently varies in different serums in affinity for lipoids in various extracts. For this reason, and especially if employing cholesterinized extracts, it is preferable to use from three to five different extracts with each serum, the total reactions indicating more conclusively the result than one "antigen" alone.

14. Kolmer, J. A., and Casselman, A. J.: Jour. Med. Research, July, 1913.

(c) Cholesterinized Extracts in the Serum Diagnosis of Syphilis: The cholesterinized extracts already mentioned of normal organs and syphilitic liver were used in examining 287 serums and nine cerebrospinal fluids, plain alcoholic and acetone extracts and acetone-insoluble lipoids being used at the same time for comparison. Of this number of specimens 139 yielded positive reactions.

The results with a cholesterinized alcoholic extract of beef heart, compared to alcoholic extracts of syphilitic liver, are as follows:

1. In 63, or 45.3 per cent. of cases, the reactions were equal to those obtained with the plain alcoholic extract of syphilitic liver.

2. In 41, or 29.4 per cent. of cases, the reactions with the cholesterinized extract were stronger.

3. In 2, or 1.4 per cent. of cases, the reactions with the cholesterinized extract were weaker. Both cases were diagnosed paresis.

4. In no instance occurred a negative reaction with the cholesterinized extract, with a positive result with the control "antigens."

5. In 32, or 23.0 per cent. of cases, the cholesterinized extract yielded a positive result, whereas with the alcoholic extract of syphilitic liver the reactions were negative. These results are worthy of further analysis, especially in view of the fact that we found this extract to give slight inhibition of hemolysis with normal serums.

(a) Of these thirty-two cases, fifteen yielded a weak reaction with the cholesterinized extract, showing about 25 per cent. inhibition of hemolysis (+) as follows:

Two cases of paresis. Positive history in one case.
One case of tabes dorsalis.
One case of tuberculous enteritis. History not obtainable.
One case of optic neuritis.
One case of secondary syphilis.
Two cases of spastic hemiplegia. History not obtainable.
One case of latent lues. Positive history.
One case of lues of three years' duration; thorough treatment with salvarsan and mercury.
One case of recurrent herpes of mouth (patient of Dr. J. F. Schamberg), of one year's duration, resistive to ordinary therapeutic measures. Since Hutchinson has directed attention to the fact that these cases are frequently leutic, Dr. Schamberg is administering antiluetic treatment.
One case of hereditary lues.
Three cases of psoriasis. History of infection denied.
One case of recurrent abortion. History of infection denied.

(b) Six cases yielded slightly stronger reactions, about 50 per cent. inhibition (+ +), as follows:

One case of tabes dorsalis. Positive history.
One case of incipient tabes. Positive history.
One case of hemiplegia. Positive history.
Two cases of spastic hemiplegia. History not obtainable.
One case of hereditary lues.

(c) Two cases yielded strongly positive reactions (+ + +), about 75 per cent. inhibition, as follows:

One case of hemiplegia. History not obtainable.
One case diagnosed tuberculosis of lungs. Positive history.

(d) Eight cases yielded absolute positive reactions (+ + + +) or 100 per cent. inhibition of hemolysis. These reactions are most striking and clearly illustrate the tendency of cholesterinized extracts to give strong inhibition of hemolysis in the presence of but small amounts of syphilis "reagin."

One case of secondary syphilis. History positive.
One case of tertiary syphilis. History positive.
One case of hereditary syphilis.
One case of paresis. History not obtainable.
One case of tertiary syphilis (ulcerating gummata).
Two cases of hemiplegia with positive histories.
One case of cirrhosis of the liver. Patient of Dr. Gwyn's. History negative. Autopsy as reported by Dr. Gwyn showed no evidences of lues.

These results would indicate that any serum showing 50 per cent. or more inhibition of hemolysis may be regarded as luetic. In a number of cases thorough treatment with salvarsan and injections of a mercurial preparation has resulted in a strongly positive serum being converted into an absolutely negative one as tested with all antigens, including the cholesterinized extracts. The troublesome cases are those showing 25 per cent. or less inhibition of hemolysis with cholesterinized extracts and with complete hemolysis with plain extracts. In such instances, if there is a history of infection, we report the reaction as positive. If there occurs a similar slight inhibition with the plain extracts the case is almost certainly luetic. The most striking results, however, are those showing absolute inhibition of hemolysis with the cholesterinized, and complete hemolysis with the plain extracts. The results would indicate that the majority of these cases are to be regarded as luetic although it is necessary to continue the study into a larger group of cases, controlled by careful histories and autopsies.

Our cholesterinized alcoholic extracts of human and pig heart proved less sensitive than the extract of beef heart; i. e., they yielded but 5 per cent. pseudo-reactions with normal serums (one out of twenty serums tested) and did not yield quite as many positive reactions with the serums tested.

1. In 52.9 per cent. of cases the reactions were equal to those obtained with alcoholic extract of syphilitic liver.

2. In 29.3 per cent. of cases the reactions were stronger.

3. In no case were the reactions weaker.

4. In three cases serums yielded positive reactions with the cholesterinized extracts and were negative with the control extracts.

One case (+) specific optic neuritis.
One case (++) tertiary lues.
One case (++++) tertiary lues. History positive.

From the fact that we have found these extracts to be less likely to yield pseudo-reactions we rely more on them than the cholesterinized beef heart extract.

(e) Influence of Cholesterin on the Antigenic Properties of Extract of Syphilitic Liver: It may be stated in general that the addition of cholesterin to alcoholic and acetone extracts of syphilitic liver increases the antigenic value so that results with these "antigens" are similar to those obtained with the cholesterinized extracts of heart or normal liver. The addition of cholesterin does not seem to render these extracts any more specific than the cholesterinized extracts of normal organs, and they are just as likely to give minor degrees of inhibition of hemolysis with a small percentage of normal serums. The addition of cholesterin to a solution of acetone insoluble lipoids in methyl alcohol results essentially in a mixture of lecithin and cholesterin and the sensitivity is increased, but the difference in sensitiveness is not quite so marked as between the plain and cholesterinized alcoholic extracts.

SUMMARY

1. The syphilis reaction is probably due to the inactivation of complement by means of a reactionary product, "reagin," or the so-called syphilis antibody, in the presence of a suitable lipoid, the phenomenon being known as complement deviation or fixation.

2. While this lipodophilic "reagin" is not entirely a specific product of the *Treponema pallidum*, similar "reagins" being present in the serums of persons infected with yaws and leprosy, it is possible that the question of specificity may be settled by further chemical and biological studies of the lipoids, especially of tissues infected with *Treponema pallidum*. Thus extracts of syphilitic liver possess a higher antigenic value than extracts of normal liver. It is true that "antigens" of normal liver will give a positive reaction in most cases of active syphilis, but the degree of reaction in these same cases and especially with latent or actively treated cases, will be less than with alcoholic extracts of syphilitic liver. The difference is probably due to a difference in the lipoid content of the extracts, and it is possible that the *Treponema pallidum* may alter the lipoids of the liver to this extent. Plain alcoholic extracts of human, pig or beef heart possess higher antigenic value than similar extracts of normal liver, due probably to the extraction of more cholesterin. The addition of cholesterin to any or all of these extracts increases their antigenic properties. With acetone-insoluble lipoid "antigen" this difference is not so marked, due in part to the fact that such an extract is

composed largely of lecithin, which in itself possesses a high antigenic value.

3. Table 3 expresses the relative values of the various extracts in the practical serum diagnosis of syphilis, taking a suitable alcoholic extract of syphilitic liver as a standard for comparison. It must be observed, however, that the cholesterinized extracts are more sensitive than the plain alcoholic extracts of syphilitic liver.

TABLE 3.—COMPARATIVE ANTIGENIC PROPERTIES OF VARIOUS EXTRACTS

Extracts	Antigenic Properties Compared to Alcoholic Extracts of Syphilitic Liver				
	Equal	Stronger	Weaker	Neg. (pos. with Alc. Ext. Syph. Liver)	Pos. (Neg. with Alc. Ext. Syph. Liver)
Cholesterinized alcoholic extract of human and pig heart	52.9	29.3	0.	0.	17.0
Cholesterinized alcoholic extract of beef heart	45.3	29.4	1.4	0.	23.0
Acetone-insoluble lipoids	73.0	10.8	0.7	3.2	1.8
Alcoholic extract pig and beef heart	71.1	1.9	13.4	5.7	7.6
Acetone extract syphilitic liver	68.7	4.4	18.9	6.6	1.3
Alcoholic extract normal liver	73.2	0.	23.5	3.5.	0.

In the order of efficiency in the practical serum diagnosis of syphilis we would arrange the various extracts as follows:

1. Cholesterinized alcoholic extracts of human, pig and beef heart, named in the order of efficiency and safety. It should be remembered that these extracts may yield slight degrees of inhibition of hemolysis with normal serums and must therefore be carefully controlled. Cholesterinized alcoholic extracts of syphilitic liver have the advantages of cholesterin and any additional product of the *Treponema pallidum* which may be present.

2. Plain alcoholic extracts of known syphilitic liver.

3. Acetone-insoluble lipoids (Noguchi).

4. Plain alcoholic extracts of human, pig and beef heart.

5. Acetone extract of syphilitic liver.

6. Plain alcoholic extract of normal liver.

Best results are secured in the practical serum diagnosis of syphilis by using several "antigens" with each serum, including plain and cholesterinized extracts. This increases the amount of work and the

quantities of the various components of the reaction, but results warrant the former and the latter is readily overcome by using just half the quantities of Wassermann's original technic. Thus 0.1 c.c. of serum may be used with each "antigen" instead of the usual 0.2 c.c., the quantities of complement, amboceptor and corpuscle suspension being equally divided. In this manner 1.0 c.c. of serum (2 to 3 c.c. blood) will be sufficient for conducting the Wassermann and Noguchi reactions with at least two to four "antigens," including the usual serum controls.

We wish to express our thanks to Dr. Jay F. Schamberg, and also to Dr. W. Hickson of the Vineland Training School, for many serums and careful histories of patients.

Just before sending the manuscript to the publishers we noted the paper of Walker and Swift, Jour. Exper. Med., 1913, xviii, 75, in which they conclude that cholesterinized extracts fulfill the requirements of a standard antigen.

STUDIES ON THE CIRCULATION IN MAN

IX. THE BLOOD-FLOW IN THE HANDS (AND FEET) IN CASES IN WHICH OBVIOUS ANATOMICAL DIFFERENCES EXIST *

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In this paper and succeeding ones I propose to continue the description and discussion of the results obtained in clinical cases already begun[1] in papers VI and VIII.

GENERAL REMARKS

A portion of the material studied consisted of patients in the Dispensary of Western Reserve University and Lakeside Hospital, referred to in the protocols simply as the Dispensary. The major portion of the material was from the wards of the City and other hospitals. A few cases were placed at my disposal from the private practice of friends. This is pointed out because comparable results are much more easily obtained in successive observations on hospital patients whose surroundings are fairly constant, than on dispensary or private patients. At any rate, in order to obtain comparable results, fewer precautions are necessary in the case of the hospital patients. In particular, the influence of the external temperature, the factor which of all others among the external conditions is most apt to influence the results, is much more easily controlled in the case of the hospital patients, especially in winter. The observations on the latter were made in a room in the hospital to which the patients were brought in the wheel chair, or the movable bed; or to which, if well enough, they walked. As is true for many kinds of physiological clinical examination, the observations are more satisfactorily made in a separate room than in the open wards. Where the external conditions are controlled and the clinical state of the patient has not altered noticeably, the results of the blood-flow measurements from day to day, or indeed from week to week, show a very fair and often a surprising degree of constancy. Not only is the hospital patient in an environment whose temperature varies comparatively little, but his diet is also controlled and the general régimen under which he lives is relatively stable. In many of the hospital cases the approximate constancy of the flow was not only seen in the case of

* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.
* Submitted for publication July 18, 1913.
1. Stewart, G. N.: Jour. Exper. Med., 1913, xviii, Nos. 2 and 4.

one and the same hand, but also in the proportion between the flows in the two hands where a conspicuous difference existed between the two. As regards the dispensary material, care had to be taken in winter that the person was long enough in the room before the observations were begun, especially if he came to the dispensary with bare hands. It is true that if the observations were immediately begun a result would be obtained which would be correct enough for the given condition of the hands, but it would be useless as an expression of the flow under the approximately standard conditions which have to be established if comparison of the flow in the same patient at different times or in different patients is proposed. In summer the factor of external temperature presents no greater difficulty in dealing with dispensary than with hospital patients.

In addition to the clinical interest which attaches to the measurements in the individual cases dealt with in this paper, the material was chosen partly as a test of the technic of the method, as in many of the cases the qualitative difference between the two hands could be foreseen from the anatomical difference which existed.

In Steve S., a man 21 years old, with healing burns on both hands, but more extensive on the right, the flow was 7.04 grams per 100 c.c. per minute for the right hand and 5.44 grams for the left hand (for the last nine minutes in the calorimeters), with an average room temperature of 25. The burned areas on both hands were quite red, and taking the whole surface of the hands into account the vascularity of the superficial layers must have been considerably greater in the right than in the left hand. In both hands many blood-vessels in the new tissue must be nearer the surface than in the normal hand, a point of interest in connection with the technic of the method.[2] In spite of the red color, both hands feel rather cold to the touch, and this agrees perfectly with the tardiness[3] with which the thermometers rose at first and with the calculated blood-flow, which for the man's age and the room temperature, is subnormal. The redness is due to the number of capillaries in the healing areas and the fact that they lie just under the surface, not to a great flow of blood through widely dilated vessels. The case presented the opportunity of

2. Heart, 1911, iii, 55.

3. This tardiness is expressed in the calculated flow for the first eight minutes of immersion in the calorimeters, which is only 3.74 grams per 100 c.c. per minute for the right, and 2.49 grams for the left hand. The fact that the ratio of the flow in the left hand to that in the right is 1:1.50 for the first eight minutes, while it is 1:1.29 for the last nine minutes, in the calorimeters, indicates clearly that the increase in flow in the last period was not due to a central cause (increase in the driving power of the heart) which would have affected the two hands equally, but to a peripheral cause (removal of vasoconstriction which happened to be proportionately greater in the left hand at the beginning of the immersion in the calorimeters than later on).

studying the flow in blood-vessels which have not long existed and whose vasomotor connections may be still incomplete or immature. Immersion of the left hand in warm water caused a good increase, and subsequent immersion of the left hand in cold water a marked decrease in the flow in the right hand. The persistence of both reflexes was remarkable. Another peculiarity not observed in any other case was that the temperature of the right hand calorimeter during the immersion of the left hand in the warm or cold water, showed abrupt changes, for instance,

TABLE 1.—Calorimeter Test of Steve S.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
3:33½	29.92	29.84	.....	3:55	30.32	
3:37	29.90	29.88	.....	3:56	30.37	Room 24.8 C.
3:38	29.91	29.90	25.3	3:57	30.495	
3:39	29.92	29.905	.....	3:58	30.505	
3:40	29.93	29.915	.....	3:59	30.53	
3:41	29.95	29.925	.....	4:00	30.64	
3:42	29.97	29.925	.....	4:01	30.64	
3:43	29.99	29.93	25.0	4:02	30.67	
3:44	30.01	29.935	.....	4:03	30.75	
3:45	30.015	29.945	.....	4:04	30.82	Room 24.9 C.
3:46	30.05	29.97	.....	4:05	30.86	
3:47	30.10	29.99	.....	4:06	30.88	At 4:06 left hand put in water at 10 C.
3:48	30.11	30.025	.....	4:07	30.87	
3:49	30.16	30.05	.....	4:08	30.88	Room 24.8 C.
3:50	30.20	30.07	24.6	4:09	30.89	
3:51	30.215	30.12	.....	4:10	30.99	
3:52	30.28	30.14	.....	4:11	30.98	
3:53	30.295	30.15	.....	4:12	30.97	
3:54	30.305	30.18	.....	4:13	30.98	
....	.....	.....	.....	4:14	30.995	Hand out of cal. at 4:14.
....	.....	.....	.....	4:27	30.88	At 4:27 L. is at 29.94 C. Room 24.2 C.

Cooling of calorimeters, R., 0.115 degrees in thirteen minutes; L., 0.24 degrees in thirty-three minutes. Volume of right hand in calorimeter, 328 c.c.; left, 340 c.c. The hands, especially the right, could not be made to hang vertically in the calorimeters owing to adhesions. The volumes given represent the portions of the hands actually inside the calorimeters. Water equivalent of calorimeters with contents, R., 3,357; L., 3,367. Rectal temperature, 37.3 C.

a sudden rise of the thermometer between the third and fourth minutes of immersion of the left hand in the cold water — not succeeded by any further rise. The patient denied that his hand ever touched the thermometer, and from the position of the thermometer in the calorimeter contact of the hand with it can scarcely occur, unless the hand is executing extensive groping movements, of which there was no sign in these observations. The most plausible explanation of the phenomenon would

seem to be that in the new blood-vessels, although the vasomotor connections had been established, there is still an abnormal vasomotor instability. The intensity of the total reaction may be due either to hyperexcitability of the receptive surfaces of the left hand (afferent path) or to hyperexcitability of the newly-formed vasomotor endings including the muscle of the new blood-vessels (efferent path) or to both. The warm water was purposely made 3 degrees lower, and the cold water 2 degrees higher than usual, lest pain should be caused. But he did not feel any pain.

Steve S., aged 21, a sailor, was burned November 4, 1911, by the bursting of a steam pipe on a steamer. He was unconscious for a fortnight. The face, including the ears, the neck, the back, the knees and both hands and arms were burned. The sight of the right eye was destroyed. He was admitted to the City Hospital Feb. 19, 1912. Both forearms and a small portion of the upper arms above the elbow were denuded of skin and covered with jelly-like exudation and granulations. Physical examination of the heart and lungs was negative.

The blood-flow in the hands was measured April 5, 1912, at which time healing was pretty well completed, although there was still some suppuration on the right forearm, a little above the wrist. The burn on the right hand involved the palms as well as the back of the hand and there are considerable adhesions between the fingers, rendering the hand practically useless. The left palm escaped in great measure, but the back of the hand was burned. The burned areas on the hands were still quite red. Hands in bath at 3:24 p. m., in calorimeters at 3:34½; 3,015 c.c. of water in each calorimeter.[4] At 3:54 p. m. left hand put into water at 40 C. Pulse 80.

In Frank P., a man 42 years old, suffering from a malignant tumor of the right forearm, with some edema of the forearm down to the wrist, the flow in the right hand was 4.69 grams per 100 c.c. of hand per minute, in the left hand 5.31 grams, with an average room temperature of 23.2 C. The deficiency in the right hand was an actual deficiency and not merely an apparent one (owing to the reckoning in of edema liquid in the volume of the hand), since by measurement the right hand was only 3 c.c. larger than the left. It is therefore probable that the deficiency is due to the interference of the tumor with the venous return from the hand. Insofar as it is not connected with inflammatory changes, the edema is also probably caused by interference with the venous flow. In certain cases the blood-flow measurement might help to settle the question whether edema is due to obstruction on the lymph path or on the venous path. Obstruction confined to the lymphatics might cause edema without diminution in the blood-flow. Where a tumor is confined to the bone, obstruction to the flow of blood in the hand may be expected to be less marked than where it has extensively invaded the soft tissues.

Frank P., a carpenter, aged 42, was admitted to the City Hospital July 18, 1912, with a tumor mass about 10 cm. in diameter on the outer surface of the right forearm. The mass was slightly fluctuant, tender on pressure and attached

4. In all observations on the hands unless otherwise stated, this was the quantity of water in each calorimeter.

to the bone. There was some edema in the right forearm and wrist. There was another tumor mass over the upper third of the left tibia about 15 cm. in diameter. It had been incised for drainage and a muco-purulent fluid was being discharged. There was a small mass and tenderness over the upper third of the right fibula. X-ray examination showed a large rounded mass on the right forearm going deep into the tissues, as much of it below the surface as above the surface. The swellings on the left leg and upper forearm were noticed about the same time, three months before admission. They have gradually increased in size and of late have been very painful. Physical examination of the heart was negative. Thorax emphysematous and expiration prolonged. Percussion note raised in pitch and shortened on the left side, especially at the left base. Respiratory sounds diminished on the left side, where numerous rhonchi were present. Tactile fremitus diminished on the left side. The diagnosis was multiple sarcoma. The patient refused operation and left the hospital. The examination of the blood-flow was made Aug. 1, 1912. Hands in bath at 2:22 p. m., in calorimeters at 2:33 and out of calorimeters at 2:52. Pulse (sitting) 96. The day was exceptionally cool for the season.

TABLE 2.—Calorimeter Findings in Case of Frank P.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp., C.
2:32	30.16	30.14	....	2:44	30.48	30.49	23.4
2:34	30.18	30.15	22.9	2:45	30.505	30.54	....
2:35	30.205	30.175	.....	2:46	30.53	30.58	23.2
2:36	30.23	30.20	23.1	2:47	30.57	30.62	....
2:37	30.26	30.21	.....	2:48	30.595	30.665	....
2:38	30.27	30.26	23.1	2:49	30.61	30.69	....
2:39	30.315	30.29	.....	2:50	30.64	30.72	23.0
2:40	30.35	30.33	23.1	2:51	30.67	30.75	....
2:41	30.39	30.37	.....	2:52	30.695	30.765	22.95
2:42	30.41	30.43	.....	3:09	30.485	30.565	....
2:43	30.44	30.46	.....	....	.....	.....	....

Cooling of calorimeters in seventeen minutes, R., 0.21 degrees; L., 0.20 degrees. Volume of right hand, 476 c.c.; the same for a second measurement. Volume of left hand, 473 c.c. To the eye the right hand appeared somewhat swollen, but this seemed to be an error of judgment, caused by the distinct swelling of the right forearm below the level of the tumor down to and involving the right wrist. The swelling did not descend below the wrist. Water equivalent of calorimeters with contents, R., 3,476; L., 3,473. Blood-pressure, left arm, systolic 115 (palpation), 114 (stethoscope), 80 (sound gone). Pulse (sitting) 114. Rectal temperature, 37.95 C.

A condition in which edema coincided with obstruction to the lymph-flow not involving the venous flow seems to have been realized in the case of Charles B., a man 47 years old, in whom the diagnosis of Hodgkin's disease was made. He entered the hospital with both legs and feet greatly swollen. The swelling was stationary and little if at all diminished in the morning. During his entire stay in the hospital (over five weeks) the swelling of the legs remained unchanged. There was no edema elsewhere. All accessible lymph-nodes were enlarged. The blood-flow in the right foot was 2.34 grams per 100 c.c. of foot per minute, or, allowing for

the edema fluid, 3.04 grams, and in the left foot, 2.50 grams (allowing for the edema fluid, 3.24 grams) with average room temperature 22.5 C. These flows are by no means small for the feet. Indeed, in comparison with the hand flows (2.82 grams for the right and 3.22 grams for the left hand) they are large. A certain degree of anemia, some cyanosis and dyspnea were present, and this may contribute to the small hand flow.[5] It may be supposed that this would tell equally on the blood-flow through the feet, but in the absence of special observations on this point, we cannot be certain whether the compensatory vasoconstriction in anemia is not greater in the anterior limb than in the posterior limb. It is conceivable that the circulation in the anterior limb has a closer association with the pulmonary circuit than the circulation in the posterior limb. That the hands were exceptionally liable to vasoconstriction was shown by observations on Nov. 27, 1912, which gave a still smaller flow. It is rare to find a case in which the flow per 100 c.c. of foot per minute comes out as great as the flow per 100 c.c. of hand per minute in the same individual. In the vast majority of clinical cases the hand flow greatly preponderates, and this is the invariable rule for normal persons so far as our experience goes.[6]

Interference with the local circulation would seem to be excluded in this case as a cause of the edema of the legs. It is more likely, indeed, if we take account of the hand flows, that there is a local acceleration of the blood flow in the legs, perhaps through partial paralysis of their vasoconstrictors by the pressure of the same masses, if it is an affair of mechanical pressure, as are responsible for the edema. If we confine ourself to the question, leaving out all other possibilities, whether the edema is dependent on venous or on lymphatic obstruction, the blood flow measurements give an answer in favor of lymphatic obstruction, to this extent supporting the diagnosis of Hodgkin's disease.

Charles B., lumberman, 47 years old, height 5 feet, 6 inches, was admitted to City Hospital November 8, 1912. The glands were generally enlarged, one of the inguinal glands on the left side being as big as a walnut. Both legs were edematous and covered with varices. The varicose veins, however, were of a good many years' standing, and had not increased during the present illness, which began two months before admission with pain in the back and shortness of breath. About two weeks before admission the pain recurred and he almost fainted with the pain in the back. The feet began to swell two days before admission; the left leg began to swell two days later than the right. No edema elsewhere than in the legs. He had always lived in Cleveland or the neighborhood. Has never had piles. The pain in the back was a cutting pain on both sides. There had never been gravel in the urine. The skin and mucous membranes showed slight anemia, slight cyanosis, no icterus. Thorax barrel-shaped, moves slightly more on the right side. The costal angle is obtuse, the breathing mainly abdominal. Further examination of thorax and the heart, also of

5. Stewart: Paper VI, Jour. Exper. Med., 1913, xviii, No. 2.
6. Stewart, G. N.: Paper VII, Jour. Exper. Med., 1913, xviii, No. 4.

the abdomen and rectum, negative. X-ray examination of abdomen negative. Some sclerosis of the radial artery. The reflexes were active. The urine contained albumin with a few granular casts on November 9, a trace only of albumin on November 18. On November 14 the leukocyte count was 14,000 (polymorphonuclear neutrophils 70 per cent., eosinophils 4.5 per cent., large mononuclears 5.5 per cent., small mononuclears 15 per cent., transitionals 2.5 per cent.).

TABLE 3.—Calorimeter Findings in Charles B. (Feet)

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
2:30	31.24	31.28	.....	2:47	31.38	31.465	.....
2:33	31.16	31.23	.....	2:49	31.40	31.485	22.7
2:35	31.19	31.27	.....	2:51	31.43	31.53	22.9
2:37	31.22	31.30	21.5	2:53	31.465	31.565	22.5
2:39	31.25	31.325	21.9	2:55	31.49	31.58	.....
2:41	31.29	31.365	22.1	2:57	31.42	31.55	.....
2:43	31.32	31.395	22.2	3:14	31.04	31.16	.....
2:45	31.335	31.44	22.4	....	.....	.....	.....

Cooling of calorimeters in seventeen minutes, R., 0.38 degrees; L., 0.39 degrees. Volume of right foot 1,313 c.c., of left foot 1,313 c.c. His feet were naturally not large, requiring a No. 7 shoe. Water equivalent of each calorimeter with contents, 3,694.

Hands in bath at 3:17 p. m. in calorimeters at 3:26½ and out of calorimeters at 3:45.

TABLE 4.—Calorimeter Findings in Charles B. (Hands)

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
3:25	30.80	30.73	.....	3:37	30.805	30.765	23.5
3:28	30.77	30.705	21.8	3:38	30.805	30.77	22.9
3:29	30.775	30.71	21.9	3:39	30.81	30.78	22.8
3:30	30.775	30.73	.....	3:40	30.815	30.79	22.7
3:31	30.78	30.735	22.3	3:41	30.825	30.82	22.6
3:32	30.78	30.735	22.5	3:42	30.83	30.83	22.7
3:33	30.79	30.745	23.0	3:43	30.84	30.84	.....
3:34	30.795	30.745	23.4	3:44	30.85	30.85	.....
3:35	30.795	30.755	23.7	3:45	30.86	30.855	.....
3:36	30.80	30.755	23.7	3:53	30.75	30.75	.....

Cooling of calorimeters in eight minutes; R., 0.11 degrees; L., 0.105 degrees. Volume of right hand 480 c.c.; of left 462 c.c. Water equivalent of calorimeters with contents, R., 3,479; L., 3,465. Rectal temperature 36.9 C. Blood-pressure in left arm (Nov. 27, 1912), systolic 158 (palpation), 155 (stethoscope), 95 (sound gone).

The blood-flow in the feet and hands was measured Nov. 29, 1912. The swelling of the legs, the patient said, was stationary. The varicose veins could not be seen on account of the swelling. There was no pain in the back, but he had pain in the lower abdomen a little above the level of the groin when he walked any distance. Pulse (sitting) 98. Feet in bath at 2:06½ p. m.; in

calorimeters at 2:31 and out of calorimeters at 2:55½; 2,575 c.c. of water in each calorimeter, as finally reduced in size.[7]

TABLE 5.—Calorimeter Measurements of Feet in Charles W.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
2:16	31.30	31.38	.....	2:43	31.35	30.92	.....
2:19	31.24	31.26	23.8	2:45	31.38	30.93	23.6
2:21	31.225	31.265	.....	2:47	31.41	30.945	23.4
2:23	31.21	31.11*	.....	2:49	31.44	30.955	23.8
2:25	31.21	31.055	23.3	2:51	31.475	30.975	24.1
2:27	31.205	31.02	.....	2:53	31.505	30.995	24.1
2:29	31.21	30.98	23.15	2:55	31.535	31.025	23.6
2:32	31.22	30.94	23.3	2:57	31.575	31.045	23.2
2:35	31.24	30.93	.....	2:59	31.60	31.07	.....
2:37	31.275	30.92	23.5	3:01	31.57	31.05	.....
2:39	31.295	30.92	24.0	3:14	31.37	30.87	.....
2:41	31.32	30.92	23.9	.....	.....	.....	.....

* Stirring in L. had not been thorough till now for fear of hurting the foot.

Cooling of calorimeters in thirteen minutes: R., 0.20 degrees; L., 0.18 degrees. Volume of right foot 1,203 c.c., of left foot 1,103 c.c. Water equivalent of foot calorimeters with contents, R., 3,817, L., 3,747. Hands in bath at 3:24½ p. m., in calorimeters at 3:34 and out of calorimeters at 3:45.

TABLE 6.—Calorimeter Measurements of Hands of Charles W.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
3:33	31.27	31.22	.....	3:41	31.67	31.605	.....
3:35	31.29	31.255	22.9	3:42	31.72	31.66	24.2
3:36	31.33	31.31	22.9	3:43	31.785	31.72	24.1
3:37	31.40	31.36	23.0	3:44	31.83	31.765	.....
3:38	31.465	31.425	23.25	3:45	31.895	31.82	.....
3:39	31.53	31.485	23.5	3:52	31.79	31.72	.....
3:40	31.60	31.55	23.9	.....	.....	.....	.....

Cooling of hand calorimeters in seven minutes: R., 0.105 degrees; L., 0.10 degrees. Volume of right hand 486 c.c., of left hand 470 c.c. He is right handed. There is no difference, he says, in his hands, as to strength or otherwise, nor was there any difference at the time of the "strokes." Water equivalent of hand calorimeters with contents, R., 3,484, L., 3,471. Rectal temperature 37.9 C.

He was discharged Dec. 22, 1912, able to use the left foot better, he says, than for the previous seven years.

Charles W., a clerk, aged 42, was admitted to the City Hospital October 29, 1912. He had rheumatism at the age of eight years, since which time the left leg seemed to be weaker and smaller than the right. At that time the arms and legs were somewhat swollen and extremely sensitive. He had a stroke of paralysis in 1903. He was sitting in a chair reading and found he could not

7. For details of the method of measuring the flow in the feet see Paper VII of this series.[6]

rise to walk. There were no convulsions. Both arms and legs were affected. He could not move the eyes, nor talk, and his sight was affected. No bowel or bladder trouble. In seven months he had recovered from the stroke and had no trouble in walking or in any other way until 1907, when he had a second stroke of the same kind preceded by slight dizziness, but otherwise no subjective signs. There was no disturbance of vision. It took four years for his complete recovery from the second attack and then he felt "real well." Four months before admission he fell on the sidewalk and abraded the left shin about 3 inches. It healed somewhat and the scab "raised up" and began to pain him severely, the pain shooting down the leg. He went to a hospital for four weeks and it again healed to some extent. On leaving the hospital it became worse, then healed again, but continued to be very painful. It opened again and the pain continued so that he could not sleep. There are many petechial spots on the left leg. Examination of thorax negative. Reflexes increased in the left leg. The left leg is atrophied and much smaller than the right and 1½ inches shorter. The left foot is not small, although doubtless smaller than the right. It is the lower leg which is conspicuously small. He denies lues emphatically. The Wassermann blood test was twice negative. Spinal fluid also negative, cell count negative, Noguchi negative.

The blood-flow in the feet and hands was measured Dec. 18, 1912. There was no pain in left leg. Feet in bath at 2:04 p. m., in calorimeters at 2:17½ and out of calorimetrs at 2:59; 2,775 c.c. of water in each calorimeter. Pulse (sitting) 92. He felt the feathers equally well on both legs.

I was asked to make an examination of the flow in the feet in case some light might thus be thrown on the diagnosis. The flow in the right foot was 1.89 grams per 100 c.c. per minute and in the left 1.56 grams (for the last ten minutes in the calorimeters), with an average room temperature 23.9 C. From the small deficiency in the flow in the left foot as compared with the right, it was concluded that there was no obstruction in the main arterial supply of the left leg which could account for the slow healing of the sore and for the pain in the leg. If the cause was vascular it was therefore a vasomotor affair, possibly even a local vasoconstriction due to the pain itself. Undue susceptibility to vasoconstriction might account for the relatively small flow in both feet. The slow increase in the flow in the left foot at the beginning of the observations supports the view that it was peculiarly susceptible to vasoconstriction. The consequence of this stubborn vasoconstriction is that the ratio of the flow in the left foot to that in the right for a period of twenty-four minutes in the calorimeters, beginning seventeen and one-half minutes from the first insertion therein, is 1:1.55, while for the last ten minutes in the calorimeters it is 1:1.21. The cause of the small flow was not a central one (deficiency in the driving power of the heart), since the flow in the hands was normal (10.62 grams for the right hand per 100 c.c. per minute and 10 grams for the left with room temperature 23.6 C.).

Philip D., a street laborer, 47 year old, a dispensary patient. Weight 170 pounds; height 5 feet, 10½ inches. His right arm was shorter than the left from inflammatory rheumatism, he said, 13 years previously. Some arteriosclerosis. He had had pneumonia, pleurisy and rheumatism. He had a troublesome cough and coughed a good deal while his hands were in the calorimeters

He had a great many clothes on but the hands were not warm. The blood-flow in the hands was examined Dec. 20, 1910. At 2:23 p. m. hands put in bath; at 2:32 in calorimeters, and at 2:45 taken out of calorimeters. He was in a hurry to get back to work and therefore his hands were left only nine minutes in the bath; 3.050 c.c. of water in each calorimeter. This was one of the earlier cases examined and the calorimeter and room temperature was 19.1 C. Bath temperatures were lower than are usually employed now.

TABLE 7.—Calorimeter Measurements in Case of Philip D.

Time	Right	Left	Time	Right	Left
2:30	29.49	29.44	2:40	29.50	29.50
2:33	29.40	29.38	2:41	29.53	29.61
2:34	29.41	29.38	2:42	29.59	29.60
2:35	29.40	29.38	2:43	29.61	29.63
2:36	29.41	29.40	2:44	29.66	29.70
2:37	29.41	29.40	2:45	29.69	29.70
2:38	29.43	29.42	2:55	29.54	29.56
2:39	29.47	29.45	....	.....	.....

Cooling of calorimeters in 10 minutes: R., 0.15 degrees; L., 0.14 degrees. Volume of right hand in calorimeter, 385 c.c., of left, 375 c.c. Pulse (standing) 68. Mouth temperature 37.0 C.

The flow in the right hand, which showed no wasting, was 7.05 grams per 100 c.c. per minute; in the left 7.41 grams, with the rather low room temperature of 19.1 C. These flows are fair for his age and clinical condition. As his haste to return to work did not permit a sufficiently long examination, and no opportunity to repeat the observations occurred, it is not possible to say whether the small deficiency in the right hand flow is permanent and associated with the shortening of the arm.

Some interesting cases in which obvious differences between the two hands exist were found in unilateral inflammations. Of these we shall cite three—one in which the inflammation was due to an infected finger, one in which it was due to gout, and a third in which it was due to a sprain.

Charles C., a teamster, aged 36, had an infection of the right hand, with considerable swelling and redness; otherwise he was in good health. The protocol has been already published.[8] The flow was 11.93 grams per 100 c.c. per minute, or allowing for the edema fluid, 13.05 grams in the right hand against 4.92 grams in the left, with room temperature at 23.8 C.

There can be no doubt that along with an increase in the flow in the inflamed hand in this case there goes a decrease in the flow in the normal hand, since 4.92 grams is an abnormally small flow for a healthy man of this age. The suggestion is that in order to provide for the increased flow in the infected area a vasoconstriction, possibly elicited reflexly through the pain nerves of the infected hand, is brought about

8. Heart, 1911, iii, 82.

elsewhere and particularly in the symmetrically placed parts on the opposite side.

However this may be, a fact of interest emerges when the vasomotor reflexes from the left to the right hand are studied. Immersion of the left hand in cold water caused scarcely any reduction of the flow in the right hand (from 11.93 to 11.15 grams, or allowing for the edema liquid, from 13.05 grams to 12.20 grams). This is a very much smaller reaction than normal, and suggests that vasoconstrictor impulses to the inflamed part are blocked, perhaps, by a local action of the bacterial products or of something produced in the reaction between them and the leukocytes on the vasomotor nerve endings. It is clear that such a block may be of importance in maintaining against casual and vagrant vasoconstrictor impulses, so to say, the full stream of blood which is so important a factor in combating the infection.

Immersion of the left hand in warm water also caused hardly any increase in the flow through the right hand beyond promptly removing the small effect of the cold water. But this is of less significance, as the vasodilatation in the infected hand was probably already nearly maximum, and it is usual to obtain a relatively small reflex vasodilatation in a hand with a large initial flow. It is, however, again of interest that the initial vasoconstriction which normally follows immersion of the contralateral hand in warm water is here absent, a further indication of a block on the vasoconstrictor path. A different picture is presented by the case of gouty (non-bacterial) inflammation in which two examinations were obtained.

Harry S., aged 50, a patient at the City Hospital. He had suffered from gout for twenty years. He had no knowledge of its having been in the family before him. His mother suffered much from rheumatism. There are tophi in the scrotum as well as in the ears. There is a trace of albumin in the urine, also some fine granular and hyaline casts. First examination of the hand flow April 3, 1912. The right wrist and hand were painful and swollen. Hands in bath at 2:20 p. m., in calorimeters at 2:32 p. m. Mouth temperature 37.1 C. At 2:44 p. m. left hand put in water at 43 C.

Second examination of hand flow July 9, 1912. The right wrist and hand were much swollen and there was considerable pain. The day was warm and muggy. Pulse (sitting) 100. Hands in bath at 2.07 p. m.; in calorimeters at 2:17 p. m. Only 2,965 c.c. of water was put into each calorimeter on account of the swelling of the right hand. At 2:30 p. m. left hand put into water at 8.3 C. He feels it very cold.

At the first examination with room temperature 24.3 C., the flow was 6.88 grams per 100 c.c. of hand per minute (or allowing for the swelling, 7.47 grams) in the right hand and 3.07 grams in the left. Immersion of the left hand in warm water caused the usual initial diminution of the flow in the right to 4.66 grams (or, allowing for swelling, 5.06 grams), followed by an increase to 9.88 grams (or, allowing for the edema, 10.73 grams), a good vasodilatation. It must, of course, be remembered that the initial flow in the right hand did not correspond with anything like

a maximal vasodilatation. It is therefore all the more significant that immersion of the left hand in cold water caused a marked and persistent decline of the flow in the right hand to 3.84 grams (or, allowing for the swelling, to 4.16 grams). There is, then, in this case of non-bacterial inflammation, no sign of vasoconstrictor block.

TABLE 8.—Calorimeter Measurements in Case of Harry S.

Time	Right	Left	Room Temp., C.	Time	Right	Notes
2:33	30.32	30.21	.....	2:51	31.11	At 2:51 left hand put in water at 8 C.
2:34	30.36	30.22	.....	2:52	31.13	
2:35	30.37	30.23	.....	2:53	31.18	
2:36	30.40	30.23	24.2	2:54	31.19	
2:37	30.43	30.23	.....	2:55	31.21	
2:38	30.49	30.24	.....	2:56	31.23	Room at 24.0 C.
2:39	30.55	30.27	.....	2:57	31.245	
2:40	30.59	30.305	24.3	2:58	31.27	
2:41	30.63	30.315	.....	2:59	31.29	At 2:59 left hand dried and wrapped.
2:42	30.69	30.33	.....	3:00	31.295	Room at 24.1 C.
2:43	30.71	30.33	.....	3:01	31.32	
2:44	30.76	30.34	.....	3:02	31.33	
2:45	30.795	.....	.....	3:03	31.37	
2:46	30.805	.....	24.5	3:04	31.395	
2:47	30.86	.....	.....	3:05	31.42	At 3:05 hand out of calorim. Room 32.7
2:48	30.92	.....	.....	3:13½	31.33	At 3.13½ L. is at 30.07 C.
2:49	30.99	.....	.....	....	.....	
2:50	31.06	.....	24.2	....	.....	

Cooling of calorimeters: R., 0.09 degree in 8½ minutes; L., 0.27 degree in 29½ minutes. Volume of right hand in calorimeter 456 c.c., of left hand 404 c.c. Pulse (sitting) 76. Water equivalent of calorimeters with contents, R., 3,460, L., 3,418.

The same fact comes out fully as well in the second examination, which was made on a very warm day with a room temperature of 29.7 C. The right hand was much more swollen at the second examination than at the first. At neither examination was there any pain in the left hand. The initial flow was 13.27 grams per 100 c.c. per minute (taking only the flow corrected for the edema liquid) in the right and 8.13 grams in the left hand. As compared with the previous examination, the flow in the left hand is, of course, proportionately more increased by the high external temperature than that in the right. It is still, however, for the temperature a distinctly subnormal flow. On immersion of the left hand in cold water, the flow in the right was diminished to 8.47 grams, a very fair reaction in the normal direction, and this was augmented to 12.82 grams, nearly the initial flow, on subsequent immersion of the left hand in warm water.

TABLE 9.—SECOND EXAMINATION IN CASE OF HARRY S.

Time	Right	Left	Room Temp., C.	Time	Right	Notes
2:16	31.39	31.30	29.7	2:34	32.535	The cold water does not feel as bad as it did.
2:18	31.47	31.42	.....	2:35	32.58	
2:19	31.55	31.445	.....	2:36	32.61	
2:20	31.625	31.48	.....	2:37	32.66	He says the cold water is now more tolerable.
2:21	31.70	31.525	29.65	2:38	32.69	
2:22	31.78	31.56	.....	2:39	32.74	At 2:39 left hand put in water at 42.8 C. Room 29.6 C.
2:23	31.87	31.625	.....	2:40	32.795	
2:24	31.94	31.66	.....	2:41	32.825	
2:25	32.03	31.73	29.8	2:42	32.89	
2:26	32.105	31.77	.....	2:43	32.955	Room 29.9 C.
2:27	32.18	31.82	.....	2:44	33.01	
2:28	32.24	31.855	.....	2:45	33.07	
2:29	32.32	31.90	.....	2:46	33.125	Room 30.0 C.
2:30	32.38	31.95	.....	2:47	33.195	
2:31	32.41	.....	.....	2:48	33.25	At 2:48 hand out of calorimeter.
2:32	32.47	.....	.....	3:02	33.16	At 3:02 temperature of L. is 31.825 C.
2:33	32.50	.....	29.7	....	.....	

Cooling of calorimeters: R., 0.09 degrees in fourteen minutes; L., 0.125 degrees in thirty-two minutes. Volume of right hand in calorimeters 530 c.c., of left hand 410 c.c. Rectal temperature 37.95. Water equivalent of calorimeters with contents: R., 3,519; L., 3,423. Blood-pressure left arm, systolic 114.5 (palpation), 114 (stethoscope), 85.5 (sound gone). Another observation with stethoscope, systolic 108, 88 (sound gone).

It would not be profitable to speculate on the reasons for the difference in the reflex vasomotor reactions in the two cases related further than to point out that the local infection is an acute affair, a bacterial invasion fraught with imminent peril to the organism if it be not promptly dealt with. The mechanism exists also, and in the blood, for the effective and rapid destruction of the bacteria. On the other hand, if the essential condition of the gouty paroxysm be the deposition of urates in the tissue, while an increase in the blood-stream, which does take place, may doubtless be of value in aiding the tissue to segregate the deposit so as to minimize its action as a mechanical irritant, no increase in the blood flow, however great and however sustained, will soon effect the re-solution of the deposit, which in any case is quite indifferent to the body as a whole and exposes it to no danger of invasion.

The third case was that of Martin B., a man aged 66 years, who had sprained the little finger of his left hand three days before the examina-

tion. The hand was swollen, but not greatly. He said the pain had diminished. The difference in flow between the two hands is very striking (1.7 grams per 100 c.c. per minute for the right hand and 5.2 grams for the left with a room temperature of 23.4 C.). Absolutely the flow is small in both hands, which is accounted for by the arteriosclerosis,[9] the renal disease and the age of the patient. It may be worth pointing out once more that the high systolic arterial pressure far from indicating a copious flow, is commonly the index of a high peripheral existence, coupled with a small flow. No observations were made on the vasomotor reflexes, although it would have been interesting to compare a case of traumatic non-bacterial inflammation with the case of infection (Charles C.). The complicating conditions, however, especially the arteriosclerosis, which tends to prevent marked vasomotor reflexes, rendered the case an unfavorable one for these tests. Yet there is little doubt that the small flow in the right hand is in part due to reflex vasomotor stimulation, probably from the other hand (pain stimulation?).

Martin B., a carpenter, aged 66, height 5 feet, 8 inches, weight 165 pounds, rather stout, born in Bavaria, but long in this country. Drinks considerable quantities of beer. He has been coming to the dispensary for some time. Extract from dispensary record Nov. 25, 1910: "Marked arteriosclerosis. Albumin in urine, also hyaline casts, epithelial cells, mucus and blood. No sugar. Puffiness under the eyes. Boundaries of heart dulness, upper border of third rib, right sternal margin, and 2½ fingers outside the left nipple. Emphysema." On Jan. 16, 1912, he fell and hurt his left hand, spraining the little finger. The left hand is swollen, but not greatly. He says the pain is better than it was. The blood-flow in the hands was measured Jan. 19, 1911. Systolic blood-pressure 151. Hands put into bath at 2:58 p. m., into calorimeters at 3:10 p. m., and out of calorimeters at 3:24; 3,050 c.c. of water in each calorimeter. Mouth temperature 37.38 C.; room 23.2 C.

TABLE 10.—Calorimeter Measurements in Case of Martin B.

Time	Right	Left	Time	Right	Left
3:09	29.49	29.33	3:19	29.49	29.60
3:12	29.45	29.33	3:20	29.50	29.66
3:13	29.45	29.38	3:21	29.50	29.69
3:14	29.46	29.41	3:22	29.52	29.74
3:15	29.46	29.45	3:23	29.53	29.79
3:16	29.47	29.49	3:24	29.54	29.84
3:17	29.48	29.52	3:42	29.38	29.67
3:18	29.48	29.57	....	.....	.....

Cooling of calorimeters in 18 minutes: R., 0.16 degrees; L., 0.17 degrees. Volume of right hand 490 c.c., of left hand 497 c.c. He is right handed. Water equivalent of calorimeters with contents, R., 3,522, L., 3,528. Room temp., 23.6 C.

The influence of pain in diminishing the flow in the hands when the inflamed area is not situated in the hands themselves, is perhaps illustrated in the case of George S.

9. See Paper XI (unpublished) of this series, The Archives Int. Med., 1914.

George S., a teamster, aged 37 years, was admitted at the dispensary Jan. 31, 1911, suffering from an inflamed right elbow (acute articular rheumatism). He first felt pain in the elbow three weeks previous to admission suddenly while he was sitting in a saloon. The swelling came on afterwards. He had no knowledge of any injury. The elbow on admission was hot and swollen. He had used alcohol and tobacco to excess. He had delirium tremens in July, 1910. He had chancre four years previously, but denied gonorrhea. He had swelling of four toes of left foot for three days four months previously. The heart was normal. On February 2 the arm was not quite so red, and on February 6 it was much better. The hand and forearm were quite unaffected. His height was 5 feet, 7 inches; weight 156 pounds.

The flow in the hands was examined Feb. 2, 1911. The day was cold and he had no gloves on when he came to the dispensary. Pulse (sitting) 92. Hands in bath at 2:40 p. m., in calorimeters at 2:50 and out of calorimeters at 3:06. The experiment was shorter than had been intended as he said he was suffering so much pain that he could not keep the right hand in any longer. There was 3,050 c.c. of water in each calorimeter.

TABLE 11.—Calorimeter Examination in Case of George S.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
2:49	29.74	29.79	.....	3:00	29.75	29.76	22.3
2:51	29.69	29.73	.....	3:01	29.77	29.80	.....
2:53	29.69	29.73	22.2	3:02	29.79	29.80	.....
2:54	29.70	29.74	.....	3:03	29.80	29.81	.....
2:55	29.69	29.73	.....	3:04	29.82	29.83	22.3
2:56	29.70	29.74	.....	3:05	29.83	29.83	.....
2:57	29.71	29.74	.....	3:06	29.85	29.86	.....
2:58	29.72	29.74	.....	3:17	29.72	29.73	22.2
2:59	29.73	29.74	.....	.....	.....	.....	.....

Cooling of calorimeters in eleven minutes: 0.13 degrees for R. and L. Mouth temperature 37.05 C. Volume of right hand in calorimeter, 487 c.c., of left hand 456 c.c. Water equivalent of calorimeters with contents, R., 3.520; L., 3.495.

As was to be expected from the fact that the inflammation, although unilateral, does not involve either hand, the blood-flow is approximately the same in the two hands (3.18 grams per 100 c.c. per minute for the right hand and 3.40 grams for the left hand, with room temperature 22.2 C.). So far as it goes the deficiency in the right hand as compared with the left, if the markedly subnormal flow for the age of the patient is determined in any important degree by reflex impulses from the inflamed area, may be due to the closer anatomical connection of the afferent paths from the right elbow with the efferent paths to the right than with those to the left hand. Another factor which probably contributed to the small flow is that the man came to the dispensary on a cold day without gloves and could not be kept for a sufficiently long interval before the examination. Also he was a teamster, accustomed to the exposure of the hands to cold, and there is some evidence that these

"cold-adapted" hands require an unusually long time to respond to our standard conditions of temperature.

It may be instructive to cite here a case in which one hand remained persistently swollen without any symptoms or history of inflammation.

Miss M. F., 34 years of age, 5 feet, 2 inches in height, a cook in a restaurant, was seen at the dispensary Feb. 16, 1911, on which day the blood-flow in the hands was measured. The left hand was permanently swollen to a moderate degree. The swelling came on about two years previously and had not varied to any extent. There was no pain or discomfort and no loss of power, but she felt the left hand to be colder than the right, especially in summer. There was a transverse scar on the radial side of the back of the wrist which she said was due to the lancing of a boil about the time the swelling came on. She did not connect the lancing of the boil with the swelling, to which, indeed, she paid no attention, coming to the dispensary not on her own account, but with a friend. Nevertheless on cross-examination she said she felt pretty sure that there was no swelling until after the boil had been lanced. On the day of examination both hands felt rather cold, and to the touch there was no difference between them. Pulse 110 (sitting). Hands in bath at 3:53 p. m., in calorimeters at 4:04 and out of calorimeters at 4:23. Mouth temperature 37.02 C.

TABLE 12.—Calorimeter Measurements in Case of Miss F.

Time	Right	Left	Room Temp., C.	Time	Right	Left	
4:03	29.96	29.50	.....	4:15	30.11	29.71	.....
4:05	29.95	29.50	.....	4:16	30.12	29.72	.....
4:06	29.96	29.50	23.9	4:17	30.13	29.75	.....
4:07	29.96	29.52	.....	4:18	30.18	29.81	.....
4:08	29.97	29.53	.....	4:19	30.19	29.83	.....
4:09	29.99	29.56	.....	4:20	30.22	29.85	.....
4:10	30.01	29.60	.....	4:21	30.25	29.88	.....
4:11	30.04	29.62	.....	4:22	30.28	29.90	.....
4:12	30.06	29.65	.....	4:23	30.29	29.91	.....
4:13	30.07	29.68	.....	4:40	30.11	29.73	.....
4:14	30.09	29.70	24.1	.....	.....	.....	.....

Cooling of calorimeters in seventeen minutes, 0.18 degrees for R. and L. Volume of right hand in calorimeter, 355 c.c., of left hand 380 c.c.

The flow in the right hand comes out 4.81 grams per 100 c.c. per minute, in the left 4.78 grams (or, allowing for the probable amount of edema liquid, 5.4 grams), with room temperature at 24 C. The contrast with the cases of inflammation is striking. The flow in the affected hand is somewhat more copious than in the other, indicating that the cause of the edema is probably not obstruction to the venous return. In view of the coincidence between the appearance of the edema and the opening of the boil, it seems most natural to connect the swelling with injury to the radial nerve not as yet recovered from, since there is no indication of any infection of the lymphatics at that time. It is true that Simons[10]

10. Simons: Arch. f. Physiol., 1910, p. 559.

has stated that the radial nerve does not carry vasomotor fibers to the hand. But even if this be the case, and the evidence is by no means conclusive, this does not preclude the production of permanent vasomotor effects through an injury to a nerve. Infection of the nerve path at the seat of injury, as might occur if the nerve were divided through the boil, might delay regeneration. Thrombosis of veins or lymphatics might also be thought of, but with the free anastomosis it is difficult to see how this could cause permanent edema. The fact that it was in summer that she felt the left hand cold in comparison with the right indicates that the vasomotor response to external heat is less perfect than in the normal hand. A case of edema in the foot and leg probably connected with a traumatic injury will be referred to in another connection (Paper XI of this series, case of Charles H.).

In this connection may be mentioned experiments in which the flow was tested in a normal man (M. C.) after bandaging one hand so as to cause temporary anemia of the part, or after bandaging one forearm so as to cause temporary congestion of the hand. In both cases the bandage was removed just before the hands were put into the calorimeters.

M. C., a normal man 22 years old, height 5 feet, 10 inches, weight 146 pounds (stripped). April 17, 1911, an experiment was conducted to test the effect of bandaging the hand on the blood-flow after removal of the bandage. At 3:38 p. m. began bandaging the left hand from the finger tips upward with a rubber bandage (Martin's). Bandaging was completed at 3:39½ p. m., at which time both hands were immersed in the bath, the temperature of which was 30.2 C. At 3:50 p. m. the hands were put into the calorimeters, the bandage having been rapidly removed from the left hand while it was still kept in the bath. At 4:04 p. m. the hands were removed from the calorimeters. Volume of right hand in calorimeter 473 c.c., of left hand 448 c.c. Rectal temperature 36.9 C.

TABLE 13.—Calorimeter Measurements in a Normal Individual After the Hands Had Been Bandaged

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
3:48	29.99	30.04	23.8	3:59	30.31	30.44	24.4
3:51	30.02	30.08	.....	4:00	30.37	30.50	.....
3:52	30.06	30.15	.....	4:01	30.41	30.54	24.4
3:53	30.09	30.21	24.4	4:02	30.45	30.59	.....
3:54	30.12	30.23	.....	4:03	30.49	30.61	24.4
3:55	30.16	30.28	.....	4:04	30.52	30.64	.....
3:56	30.19	30.32	.....	4:04½	30.52	30.64	.....
3:57	30.22	30.35	.....	4:10½	30.47	30.60	24.2
3:58	30.28	30.41	.....	.....	.....	.....	.....

Here the flow per 100 c.c. per minute in the right hand works out at 6.25 grams and in the left hand at 7.04 grams for thirteen minutes in calorimeters. For the first 11 minutes of this period the calculated flows

are 6.26 grams per 100 c.c. per minute for the right hand and 7.45 grams for the left. The flow in the previously anemic hand is therefore increased to a moderate degree. Probably the increase is somewhat greater than it appears to be from these figures, since the flow per 100 c.c. per minute in M. C. is nearly always somewhat less for the left than for the right hand. In both hands the flow is less than usual for this man, as the hands had been long used for blood-flow observations on the same afternoon, and this causes vasoconstriction.

M. C., May 4, 1911. Experiment on the effect of bandaging the forearm on the flow in the hand after removal of the bandage. The left forearm was bandaged from above downward with a Martin's bandage. The bandaging was begun immediately below the bend of the elbow and carried down nearly to the upper pencil mark on the wrist, the arm being all the time in the dependent position. The hand was well filled with blood before the application of the bandage was begun and the bandage was tight enough to retain the venous blood without greatly affecting the arterial flow.

At 2:37 p. m. the hands were put into the bath and at 2:47 into the calorimeters, the bandage having been rapidly removed from the left forearm just before the hands were taken out of the bath. The hands were taken out of the calorimeters at 3:06 p. m. Pulse (sitting) 90. Cooling of calorimeters in nine minutes: R., 0.115 degrees; L., 0.11 degrees. Volume of right hand in calorimeter 486 c.c., of left 470 c.c. Water equivalent of calorimeters with contents, R., 3,484, L., 3,471. Rectal temperature 37.2 C.

TABLE 14.—Calorimeter Measurements After Bandaging the Forearm

Time	Right	Left	Notes	Time	Right	Left	Notes
2:45½	29.54	29.63		2:58	30.58	30.47	Room 23.2.
2:48	29.61	29.66	He feels left hand warmer than right.	2:59	30.67	30.54	
2:49	29.72	29.75		3:00	30.74	30.61	Left now feels water cool the whole time of stirring like right, but not as distinctly as right.
2:50	29.81	29.84					
2:51	29.90	29.92	Right hand feels water cool when stirred, but not left. Left feels tired.	3:01	30.83	30.69	
2:52	29.99	29.98		3:02	30.93	30.76	Now feels no difference in warmth of the two hands, but left still a little tired.
2:53	30.11	30.07	Room 23.3.				
2:54	30.17	30.13					
2:55	30.29	30.25	Left still feels warmer than right.				
2:56	30.41	30.34		3:03	31.01	30.83	
2:57	30.47	30.40	Left feels water only when stirring is begun.	3:04	31.09	30.90	Room 23.2.
				3:05	31.17	30.94	
				3:06	31.235	31.01	The hands now feel the same.
				3:15	31.12	30.90	Room 22.8.

For the first nine minutes in the calorimeters the flow comes out 12.86 grams per 100 c.c. per minute for the right hand, and 11.61 grams for the left. For the second nine minutes the flows are 13.31 grams, and 10.96 grams for the right and left hands, respectively; for the whole

eighteen minutes, 13.12 grams and 11.26 grams. The disproportion between the flows in the two hands cannot be due to the deeper parts of the left hand having more nearly acquired the temperature of the bath owing to the impeded circulation and being then heated up by the blood during the first part of the period of immersion in the calorimeters. For the disproportion is greater in the second than in the first nine minutes. The combined flow in the two hands remains practically constant throughout.

In the experiment of May 24, 1911, on the same man, the effect of moderate compression of the veins by a rubber band kept on one forearm during the observations is illustrated. Although the diminution in the flow is distinct, it is far less than might have been expected from the swelling of the veins in the hands. The reason is that th venous pressure quickly rises to the point at which blood again passes freely heart-wards under the band. Evidence will be brought forward in the next paper (Paper X) that some degree of venous engorgement in certain cardiac lesions in which the beat of the heart is still strong and orderly, the myocardium not having seriously deteriorated, may even be associated with an increased hand flow, the rise of venous pressure, which is general, not local as in the experiment under discussion, being more than compensated by the concomitant rise in the arterial pressure and the widening of the vascular path.

M. C., May 24, 1911. Pulse (sitting) 87. Hands in bath at 2:29 p. m., in calorimeters at 2:39½, out of calorimeters at 3:10. Mouth temperature 36.7 C. At 2:48½ put band on right forearm about 8 cm. above the upper mark. The band was made of rubber tubing. It compressed the veins without affecting the radial pulse so far as could be felt by the finger. After it was put on the subject said his right hand felt "heavy," and later on had a kind of burning sensation. Band taken off at 3:00½ p. m. Cooling of calorimeters: R., 0.95 degrees in 9 minutes; L., 0.10 degrees in nine and one-half minutes. Volume of right hand in calorimeter, 470 c.c.; of left hand, 457 c.c. Rectal temperature 37.3 C.

For five minutes before the application of the band the flow works out at 17.98 grams per 100 c.c. per minute for the right hand, and 16.65 grams for the left, with the high room temperature of 26.9 C. For the first five minutes with the band on the right arm the flows were, respectively, 15.55 grams per 100 c.c. per minute for the right, and 15.82 grams for the left hand. For the last six minutes of application of the band the flows were 13.56 grams and 13.93 grams for the right and left hands, respectively. The original preponderance of flow in the right hand has therefore been changed by the obstruction to the venous return from the right hand to a preponderance in favor of the left. That this is not due to some accidental (vasomotor?) effect in the course of the experiment is shown by the restoration of the preponderance of the right hand when the band is removed, the flow for nine minutes coming out at 15.20 grams per 100 c.c. per minute for the right, and 14.84 grams for the left hand.

The changes in the flow in the left hand suggest that the interference with the flow in the right (local asphyxia) may have caused some compensatory vasoconstriction elsewhere, especially in the left hand, as a means of raising the arterial pressure and thus helping to overcome the obstruction.

TABLE 15.—Calorimeter Measurements with Rubber Band on Arm

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
2:39	30.29	30.33	.....	2:57	32.065	32.03	.....
2:41	30.48	30.51	26.5	2:58	32.11	32.10	26.4
2:42	30.62	30.64	.....	2:59	32.20	32.16	.....
2:43	30.76	30.78	27.1	3:00	32.26	32.225	.....
2:44	30 88	30.90	26.9	3:01	32.30	32.295	26.8
2:45	31 02	31.02	.....	3:02	32.37	32.335	.....
2:46	31.125	31.105	26.6	3:03	32.43	32.405	.....
2:47	31.22	31.205	.....	3:04	32.495	32.46	.....
2:48	31.34	31.30	.....	3:05	32.58	32.535	26.5
2:49	31.41	31.37	.....	3:06	32.65	32.61	.....
2:50	31.505	31.45	.....	3:07	32.72	32.68	.....
2:51	31.595	31.535	.....	3:08	32.785	32.735	26.9
2:52	31.68	31.63	.....	3:09	32.85	32.81	.....
2:53	31.775	31.73	26.6	3:10	32.905	32.87	.....
2:54	31.85	31.81	.....	3:19	32.81	.....	.....
2:55	31.92	31.89	.....	3:19½	.....	32.77	26.5
2:56	31.995	31.95	.....	....	.....	.....	.....

Certain cases in which congenital or at least very long standing anatomical defects existed in one hand without markedly affecting its functional power were examined. Here, as was to be expected, no great difference in the flow per 100 c.c. of hand was made out.

Helen P., a girl 21 years old, height 4 feet 11 inches, well nourished. She works with a sewing machine in a factory. She said she had rheumatism at 6 months, and St. Vitus' dance two years previous to examination. She came to the dispensary for "nervousness." She has no symptoms of chorea, but is afraid she is going to have it again. Menstruation is disturbed, her period falling too late for the past two or three months, but there is no more than the usual amount of discomfort and the discharge is not altered in quantity. She has suffered much from headache the past two or three months. Her left wrist is deformed (subluxation anteriorly), the styloid process of the ulna being very prominent. The left hand is considerably smaller and the left ulna and radius shorter than the right. This has been true for a long time, perhaps from birth. The left hand is normally formed and she uses it in all ways in which a normal hand would be used, only it is not so strong as the right hand. The left anterior limb is shorter than the right and the girth of the forearm is distinctly less to the eye. The left hand does not get cold any more than the right and does not require to be better protected in winter. The pulse at the wrist is of fair volume to the finger. The blood-flow was examined July 20, 1911, the first day she came to the dispensary. Pulse (sitting) 88. Hands in bath at 2:21 p. m.,

in calorimeters at 2:45½ p. m. The lower mark on the left wrist had to be drawn through the middle instead of at the lower border of the styloid process of the ulna, as the hand was bent somewhat to the side, and the whole hand could not otherwise have been included in the calorimeter. Mouth temperature 37.6 C.

With the rather high room temperature of 26 C. the flow in the right hand was 9.08 grams per 100 c.c. of hand per minute, in the left 8.81 grams. The vasomotor reflexes from the right to the left hand were less marked than those normally observed, but in the normal direction.

TABLE 16.—Calorimeter Measurements in Case of Helen P.

Time	Right	Left	Notes	Time	Left	Notes
2:45	30.495	30.45		3:01	30.89	
2:47	30.575	30.47		3:02	30.93	
2:48	30.60	30.51		3:03	30.96	
2:49	30.64	30.54	Room 26.0 C.	3:04	30.97	At 3:04 put right hand in water at 43 C.
2:50	30.69	30.60				
2:51	30.73	30.63		3:05	30.99	
2:52	30.775	30.65		3:06	31.005	Room 26.2 C.
2:53	30.80	30.69		3:07	31.025	
2:54	30.85	30.72		3:08	31.04	
2:55	30.89	30.74	Room 26.2 C.	3:09	31.08	
2:56	30.92	30.765	At 2:56 put right hand in water at 8.3 C.	3:10	31.11	
				3:11	31.135	Room 26.1 C.
				3:12	31.155	At 3:12 hand out of calorimeters.
2:57	.....	30.80				
2:58	.....	30.825	She feels it very cold and complains of it.	3:17	31.12	At 3:17 right is at 30.77 C.
2:59	.....	30.835	Still complains of the cold water, though it is now more tolerable.			
3:00	.....	30.87				

Cooling of calorimeters: R., 0.15 degrees in twenty-one minutes; L., 0.035 degrees in five minutes. Volume of right hand, 282 c.c., of left hand, 230 c.c.

Max H., aged 46, with spastic paralysis of the left wrist (birth palsy), showed a flow in the left hand but little less than that in the right (right hand 10.71 grams per 100 c.c. per minute, left hand 10.2 grams with room temperature 20.5 C.). These flows are perfectly normal. He uses the left hand largely in his work, that of a telegraph operator. It was obviously well supplied with blood. The protocol of the case has already been published.[10]

Marie G., 15 years old, congenitally deficient in intellect and brought on this account to the dispensary by her mother, July 20, 1911. She became violent at times and would bite her mother. On admission she was in good humor. She could read books and newspapers and did so regularly. She played the piano and easily picked up a melody which she heard. She could also write, but she was quite defective in certain points; for example, she did not understand the

10. Proc. Soc. Exper. Biol. and Med., 1910, viii, 43.

time of day. She did not walk until she was 3 years old. She had menstruated regularly for about two years prior to being seen. Her left hand was congenitally defective, the thumb being wanting; otherwise it was perfectly formed, though small. The left arm both upper and lower, was much smaller in girth than the right, and the elbow joint appeared very prominent between the two ill-developed segments. The left hand easily became cold in winter. She used it quite freely, but not so much as the right. The whole left anterior extremity was somewhat shorter than the right. The mother said the child's left leg was also affected to some extent, but this was not now noticeable in her walk. She was well grown and looked well nourished. The blood-flow in the hands was examined July 20, 1911. Hands in bath at 3:24 p. m., in calorimeters at 3:26. Mouth temperature 37.35 C. At 3:50 p. m. right hand put into water at 42.8 C. Cooling of calorimeters: R., 0.12 degrees in twenty-two minutes; L., 0.14 degrees in nineteen minutes. Pulse (sitting) 88. Volume of right hand in calorimeter, 260 c.c.; of left hand, 170 c.c.

TABLE 17.—Calorimetric Measurements of Marie G.

Time	Right	Left	Room Temp., C.	Time	Left	Notes
3:35¼	30.13	30.20	.....	3:56	30.435	
3:37	30.12	30.17	26.2	3:57	30.47	
3:38	30.125	30.17	.....	3:58	30.50	
3:39	30.145	30.19	.....	3:59	30.525	
3:40	30.16	30.18	.....	4:00	30.535	
3:41	30.185	30.21	.....	4:01	30.54	
3:42	30.20	30.22	26.5	4:02	30.56	
3:43	30.225	30.23	.....	4:03	30.565	At 4:03 right hand put in water at 13 C. She says she feels it very cold.
3:44	30.25	30.23	.....	4:04	30.59	
3:45	30.28	30.24	.....	4:05	30.60	Room at 26.3 C.
3:47	30.31	30.265	.....	4:06	30.61	
3:48	30.335	30.30	.....	4:07	30.62	
3:49	30.38	30.325	.....	4:08	30.625	
3:50	30.40	30.335	.....	4:09	30.635	
3:51	.....	30.35	26.25	4:10	30.64	
3:52	.....	30.355	.....	4:11	30.65	Hand removed from calorimeter at 4:11.
3:53	.....	30.36	.....	4:12	.....	Temp. of R. at 4:12, 30.28.
3:54	.....	30.38	.....	4:30	30.51	
3:55	.....	30.41	.....	....	.....	

With average room temperature 26.3 C. the flow in the right hand was 5.96 grams per 100 c.c. per minute, and in the left 6.6 grams per 100 c.c. per minute. The flow in the defective hand is thus somewhat greater than in the normal one, in contrast to the condition in a case of infantile paralysis in N. M., a boy 9½ years old, whose left hand was much atrophied and functionally of little use. In his right hand the flow was 15.0 grams per 100 c.c. of hand per minute against 7.6 grams in the left hand with room temperature 23.4 C. The protocol of N. M. has already been published.[10]

It has been mentioned in a previous paper[11] that the flow in the distal half of the hand is greater than in the hand as a whole, doubtless because of the greater proportion of skin in the former. A case (John B.) in which some of the fingers of the left hand had been amputated, gave the opportunity of comparing two hands, one of which had suffered a considerable loss in its distal half. The blood-flow for the last ten minutes in the calorimeters was 7.20 grams per 100 c.c. per minute for the right and 5.34 grams for the left hand, a considerable deficiency in the hand which had lost fingers. The fact that the man had a right-sided pleurisy with effusion probably does not interfere with this conclusion, but, if anything, strengthens it. For it will be shown in a subsequent paper that this condition is usually associated with a diminished hand flow on the side of the lesion and that the difference may persist after the fluid has been removed.

John B., a longshoreman aged 51, admitted to City Hospital April 28, 1913, suffering from pulmonary tuberculosis, and pleurisy with effusion on the right side. He had a severe cold in the winter and in a short time the visiting nurse said he had tuberculosis. He was a well developed, well nourished man, weighing about 185 pounds, height about 5 feet, 11 inches. No cyanosis. Dyspnea present with physical signs of liquid in right pleural cavity. The heart presents nothing abnormal. Pulse full and regular. The sputum contains tubercle bacilli. May 4, at 4 p. m., 1,500 c.c. of straw-colored fluid was removed from the right thorax. Maximum temperature following admission 100.4 F. at 4 p. m., May 5. The whole middle finger and the second and third phalanges of the index finger of the left hand had been amputated for an injury. The blood-flow in the hands was measured May 6, 1913. Pulse (sitting) 100. Hands in bath at 2:46 p. m., in calorimeters at 2:57 and out of calorimeters at 3:15 p. m.

TABLE 18.—Calorimeter Measurements in Case of John B.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
2:56½	31.32	31.27	.....	3:07	31.68	31.455	.....
2:58	31.315	31.25	24.3	3:08	31.72	31.485	.....
2:59	31.33	31.265	.....	3:09	31.78	31.51	.....
3:00	31.37	31.28	.....	3:10	31.81	31.54	24.6
3:01	31.40	31.29	24.4	3:11	31.86	31.56	.....
3:02	31.43	31.315	.....	3:12	31.90	31.59	.....
3:03	31.47	31.34	24.35	3:13	31.94	31.64	24.7
3:04	31.52	31.36	.....	3:14	32.01	31.67	.....
3:05	31.57	31.39	.....	3:15	32.06	31.72	.....
3:06	31.62	31.44	24.2	3:32	31.84	31.53	.....

Cooling of calorimeters in seventeen minutes: R., 0.22 degrees; L., 0.19 degrees. Volume of right hand in calorimeter, 564 c.c., of left hand, 515 c.c. Rectal temperature 38.32 C. Water equivalent of calorimeters and contents, R., 3.546; L., 3,507. Blood-pressure, left arm, systolic 106; 93 (sound began to diminish but not suddenly); 77 (sound gone).

11. Heart, 1911, iii, 40.

The last case to be mentioned is that of Mrs. K., a woman 68 years old in whom Dr. Carl A. Hamann had ligated the innominate and right common carotid arteries for aneurysm of the subclavian.

Mrs. K., aged 68. The innominate and right common carotid arteries were tied at Charity Hospital by Dr. Carl Hamann on Feb. 26, 1913, for aneurysm of the subclavian artery. Wiring of the sac had previously been tried without effect. March 20, 1913, the blood-flow was compared in the two hands. No pulse could be felt in the right wrist or over the right brachial. She said the right hand got cold if left uncovered with bed-clothes. When hung down the veins filled well, as well as in the left hand. She said she felt the blood going down into the right hand when she hung it down. On being emptied by stripping, the veins on the back of the right hand filled from below slowly. The right hand could execute all movements, but was weak. She spoke of the loss of power in it. There was some paresthesia (pins and needles and numbness) in the right hand, but this she had before the operation, and it had not been intensified since. The nails on the right hand were getting clubbed. She noticed that they were getting "like those of a man." The change in the nails was present before the operation, but was now more marked. First examination of the blood-flow in the hands March 20, 1913. Hands in bath at 1:50½ p. m., in calorimeters at 2:00 and out of calorimeters at 2:13. Mouth temperature 37.0.

TABLE 19.—Calorimetric Measurements in Case of Mrs. K.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
1:59	30.78	30.65	26.2	2:08	30.675	30.70	.....
2:02	30.68	30.62	.....	2:09	30.67	30.72	26.7
2:03	30.675	30.64	26.5	2:10	30.67	30.75	.....
2:04	30.67	30.65	.....	2:11	30.675	30.78	.....
2:05	30.67	30.66	.....	2:12	30.675	30.795	.....
2:06	30.67	30.67	26.7	2:13	30.685	30.82	.....
2:07	30.675	30.69	.....	2:23	30.62	30.74	.....

Cooling of calorimeters in ten minutes: R., 0.07 degrees; L., 0.08 degrees. Volume of right hand, 378 c.c.; of left hand 360 c.c. Repeated the volume measurement with the same results. The right hand was not swollen. Pulse (sitting) 124. Water equivalent of calorimeters with contents, R., 3.397; L., 3.383.

Second examination March 21, 1913. The weather was decidedly colder than on the previous day. Pulse (sitting) 100. Mouth temperature 36.5 C. Hands in bath at 2:52 p. m.; in calorimeters at 3:02 p. m., and out of calorimeters at 3:25 p. m. At 3:18 the left hand was put into water at 43 C.

The blood-flows at the first examination work out at 1.50 grams per 100 c.c. of hand per minute for the right hand and 5.32 grams for the left hand (for the last five minutes in the calorimeters) with room temperature 26.7 C. The ratio between the flows in the two hands is 1:3.54. At the second examination the flow was 1.83 grams per 100 c.c. per minute in the right hand, and 6.38 grams in the left, with room temperature 22.7 C., the ratio being 1:3.48, almost identically the same ratio as at the first examination. The increased flow in both hands is

therefore due to a central cause (better heart action, with a slower pulse?). Immersion of the left hand in warm water caused practically no change in the flow in the right. It is obvious that vasodilatation in the right hand could not be expected to materially affect the flow through the narrow and difficult collateral path. The block does not lie in the peripheral portions of the vascular path and cannot be removed by dilatation of peripheral areas.

TABLE 20.—Second Calometric Test in Case of Mrs. K.

Time	Right	Left	Room Temp., C.	Time	Right	Left	Room Temp., C.
3:01	31.00	30.99	.....	3:15	30.925	31.08	22.7
3:03	30.93	30.92	22.7	3:16	30.92	31.10	.....
3:04	30.93	30.92	.....	3:17	30.925	31.125	22.7
3:05	30.93	30.925	22.7	3:18	30.925	31.15	.....
3:06	30.93	30.925	.....	3:19	30.93	.....	22.9
3:07	30.93	30.935	22.75	3:20	30.93	.....	.....
3:08	30.93	30.95	.....	3:21	30.93	.....	22.85
3:09	30.93	30.97	22.75	3:22	30.93	.....	.....
3:10	30.93	30.985	.....	3:23	30.925	.....	22.9
3:11	30.925	30.995	22.7	3:24	30.925	.....	.....
3:12	30.925	31.01	.....	3:25	30.925	.....	22.8
3:13	30.925	31.03	22.6	3:40	30.77	30.89	.....
3:14	30.925	31.06	.....	....	.....	.....	.....

Cooling of calorimeters: R., 0.155 degrees in fifteen minutes; L., 0.26 degrees in twenty-two minutes. Volume of right hand in calorimeter 369 c.c., of left hand 342 c.c. Water equivalent of calorimeters and contents, R., 3,390; L., 3,369. Blood-pressure in left arm, systolic 136; 69 (sound gone).

July 9, 1913, a third blood-flow examination was made. The patient was much improved and was doing all her own housework. The grip of the right hand was fair, though weaker than the left. She had gained considerably in weight and her arms and hands were distinctly more plump. There was no pulse in the radial. The veins on the back of the hand filled from below when emptied and much more quickly than at the last examination. She suffered a good deal from pain in the arm and shoulder. A report from Dr. Hamann, who saw her on June 24, 1913, is as follows:

"It is altogether likely that there is pressure on the brachial plexus by the end of the clavicle (a portion of the clavicle was resected at the operation), the new formed bone (which can be distinctly felt) and the cicatrix, and removal of more of the clavicle would most likely cure or relieve her. The aneurismal sac has been consolidated and but little trace of it can be felt. There is no evidence of any intrathoracic aneurism."

The results of the third blood-flow examination are entirely favorable to this view, for they show that any disability in the right hand was not now due to deficient circulation, and that the surgeon need not be deterred from operating, if an operation seemed desirable, by the fear that the symptoms might be dependent on a poor blood-flow.

The flow in the right hand came out 8.26 grams per 100 c.c. per minute and in the left 10.69 grams, for a period of twenty-three minutes, with average room temperature 26.2 C., almost the same temperature as at the first examination. The flow in both hands was considerably increased. It must be remembered that not only was the patient much stronger than when examined before, but that instead of being brought from her bed for the observations, she had come several miles on the street car. Her pulse was strong and at the rate of 104 per minute. Both hands were larger than before (right 424 c.c., left 385 c.c.).

The fact that the collateral circulation was much freer than before is particularly shown in the increase of the ratio of the flow in the two hands from 1:3.5 to 1:1.3. It is fully as well brought out by the result of the examination of the vasomotor reflexes. Immersion of the left hand in cold water caused a great diminution in the flow in the right — for the first two minutes to 2.41 grams per 100 c.c. per minute. For the next five minutes the flow was only 6.19 grams per 100 c.c. per minute, and then began to increase abruptly. Reflex vasoconstriction, therefore, was capable of markedly altering the flow in the right hand. The relative resistance of the smaller vessels of the anterior limb and of the collateral paths leading to it has accordingly changed, and the resistance in the latter does not now make up such a large proportion of the total resistance as before.

In early brachial neuritis it is usual to see a greater flow in the hand of the affected side than in that of the sound side (partial loss of vasoconstrictor tone) and the crossed vasomotor reflex to cold is intense. It is possible that in this patient part of the increase of the flow in the right hand since the last examination is due to this factor, and the good reflex vasoconstriction agrees with this.

SUMMARY

The observations in this paper were partly undertaken as tests of the technic of the method and do not lend themselves to a complete summary.

1. In a man with healing burns on the hands the apparently great vascularity of the new tissue did not correspond to an abnormally great flow. Certain phenomena interpreted as due to a peculiar vasomotor instability of the new vessels were observed in testing the vasomotor reflexes.

2. A relatively good flow in the feet was seen in a man with great and persistent edema of both legs in whom a diagnosis of Hodgkin's disease was made. This was interpreted as indicating obstruction rather on the lymph path than on the venous path.

3. Three cases of unilateral inflammation in the hand, one bacterial and two non-bacterial (gout and a sprain) were compared. The flow in

TABLE 21.—SUMMARY OF

Case	Age	Date	Pulse-Rate	Blood-Pressure	Temperature of				Volume of Part in c.c.	
					Room	Art. Blood	Calorimeters		Right	Left
							Right	Left		
Steve S.	21	4/ 5/12	80	.....	25.0	36.8	30.14	30.06	328	340
					24.8	.....	30.59	.....	....	....
					24.8	.....	30.86	.....	....	....
Frank P. ...	42	8/ 1/12	96	114.80	23.2	37.45	30.44	30.40	476	476
Charles B....	47	11/27/12	108	155.95	22.3	36.75	30.71	30.73	478	477
		11/29/12	98	.....	22.5	36.3	31.33	31.48	1,313	1,313
					23.0	36.4	30.82	30.78	480	462
Charles W..	42	12/18/12	92	.....	23.9	37.3	31.52	31.01	1,203	1,103
					23.6	37.4	31.61	31.57	2,422	2,221
Philip D....	47	12/20/10	68	.....	19.1	37.0	29.56	29.56	1,272	1,303
Charles C...	36	2/27/11	116	.....	23.8	37.8	30.59	29.87	580	500
					23.6	.....	37.42	.....	.....	....
					23.6	.....	31.97	.....	....	....
Harry S....	50	4/ 3/12	.....	.....	24.3	37.1	30.57	30.29	456	404
					24.5	.....	30.78	.....	....	....
					24.3	.....	30.96	.....	....	....
					24.1	.....	31.12	.....	....	....
					24.0	.....	31.24	.....	.....	....
		7/ 9/12	100	111.86	29.7	37.45	31.97	31.70	530	410
					29.7	.....	32.56	.....	....	....
					29.8	.....	33.00	.....	....	....
Martin B...	66	1/19/11	.....	151.0	23.2	37.38	29.50	29.59	490	497
George S. ...	37	2/ 2/11	92	.....	22.2	37.05	29.78	29.80	487	456
Miss M. F...	34	2/16/11	110	.....	24.0	37.0	30.13	29.72	355	380
M. C.	22	4/17/11	.....	.....	24.4	36.4	30.27	30.36	473	448
		5/ 8/11	.....	.....	23.3	36.7	30.04	30.03	486	470
					23.2	.....	30.85	30.71	....	....
		5/24/11	.....	.....	26.9	36.8	31.05	31.04	470	457
					26.6	.....	31.63	31.59	....	....
					26.5	.....	32.06	32.02	....	....
					26.7	.....	32.60	32.58	....	....
Helen P. ...	21	7/20/11	88	.....	26.0	37.6	30.76	30.64	282	230
					26.1	.....	.....	30.87	....	....
					26.1	.....	.....	31.06	....	....
Marie G. ...	15	7/20/11	88	.....	26.3	37.3	30.28	30.26	260	170
					26.3	.....	.....	30.45	....	....
					26.3	.....	.....	30.6	....	....
John B. ...	51	5/ 6/13	100	106(93)77	24.4	37.8	31.82	31.56	564	515
Mrs. K.	68	3/20/13	124	.....	26.7	37.0	30.68	30.74	378	360
		3/21/13	100	136.69	26.6	.....	30.68	30.72	....	....
		7/ 9/13	104	.....	22.7	36.5	30.93	31.05	369	342
					26.2	37.0	31.89	32.03	424	385
					26.2	.....	32.39	.....	....	....
					26.4	.....	32.50	.....	....	....

* Allowing 300 c.c. for edema fluid in each foot the flow would be 3.04 for the right and 3.24

† Allowing for the probable amount of edema fluid these flows would be 13.05, 12.20, and

‡ Allowing for edema fluid these flows would be 7.47, 5.06, 10.73, 6.90, and 4.16.

§ Allowing for edema fluid these flows would be 13.27, 8.47, and 12.82.

¶ Allowing for edema fluid, 5.4.

Heat Given Off in Gram-Calories			Blood-Flow in Gm. Per Min.		Flow per 100 c.c. of Part per Min.		Notes
Right	Left	In Min.	Right	Left	Right	Left	
1,242	1,010	9	23.09	18.50	7.04	5.44	Burned hands; right worse.
2,283	....	12	34.04	.....	10.38	.....	Left hand in water at 40 C.
621	....	8	14.52	.....	4.42	.....	Left hand in water at 10 C.
2,537	2,848	18	22.34	25.15	4.69	5.31	Tumor of right forearm.
506	556	18	5.15	5.70	1.08	1.19	Hands } Hodgkin's disease
3,030	3,139	22	20.79	32.89	2.34*	2.50†	Feet } with edema of
1,159	1,282	17	13.57	14.90	2.82	3.22	Hands } legs and feet.
1,183	974	10	22.76	17.20	1.89	1.56	Feet } Trophic disturbance
486	470	9	51.62	47.03	10.62	10.00	Hands } in left leg.
385	375	7	27.14	27.80	7.05	7.41	Right arm shorter than left.
4,041	1,580	9	69.19	24.61	11.93†	4.92	Infected right hand.
2,600	....	7	64.67	.....	11.15†	.....	Left hand in water at 9.2 C.
1,845	....	5	70.33	.....	12.12†	.....	Left hand in water at 4.3 C.
1,661	684	9	31.40	12.60	6.88‡	3.07	Gout; right hand.
242	....	2	21.27	.....	4.66‡	.....	Left hand in water at 4.3 C.
1,245	....	5	45.06	.....	9.88‡	.....	Left hand still in water at 4.3 C.
312	....	2	28.98	.....	6.35‡	....	Left hand in water at 8 C.
554	....	6	17.50	.....	3.84‡	.....	Left hand still in water at 8 C.
3,096	1,899	11	57.06	33.36	10.76§	8.13	Right hand worse than before.
1,443	....	9	36.43	.....	6.87§	....	Left hand in water at 8.3 C.
1,988	....	9	55.15	.....	10.40§	.....	Left hand in water at 42.8 C.
700	2,180	12	8.20	25.87	1.7	5.20	Sprain of left hand.
710	710	7	15.52	15.54	3.18	3.40	Inflamed right elbow.
1,690	1,903	16	17.08	18.16	4.81	4.78¶	Edema of left hand.
2,118	2,244	13	29.54	31.76	6.25	7.09	After bandaging left hand.
3,380	2,950	9	62.48	54.60	12.86	11.61	After bandaging left arm.
3,066	2,499	9	66.70	51.53	13.31	10.96	Second period.
2,187	1,972	5	84.51	76.09	17.98	16.65	
1,701	1,695	5	73.11	72.31	15.55	15.82	After putting band on right arm.
1,631	1,663	6	63.73	63.67	13.56	13.93	Band still on right arm.
2,430	2,348	9	71.43	67.82	15.20	14.84	After removing hand.
1,262	1,016	8	25.62	20.28	9.08	8.81	Left hand smaller than right.
.....	852	8	.....	17.59	.....	7.51	Right hand in water at 8.3 C.
.....	787	8	.....	16.71	.....	7.26	Right hand in water at 4.3 C.
979	711	10	15.5	11.22	5.96	6.6	Congenital defect of left hand.
.....	1,034	13	.....	12.90	.....	7.59	Right hand in water at 42.8 C.
.....	388	8	.....	8.04	.....	4.73	Right hand in water at 13 C.
2,188	1,547	10	40.65	27.54	7.20	5.34	Left hand partially amputated.
162	540	5	5.69	19.16	1.50	5.32	After ligation of innominate.
278	967	11	4.44	15.23	1.12	5.32	Last five minutes in calorimeter.
373	1,179	11	6.76	21.85	1.83	4.23	Whole period in calorimeters.
3,708	4,236	23	35.05	41.17	8.26	6.38	
85	.....	2	10.24	.....	2.41	10.69	Left hand in water at 10.5 C.
532	....	9	26.27	.....	6.19	....	Left hand still in water at 10.5 C.

for the left.
13.27

the infected hand was increased, while in the normal hand it was diminished. In the case of gout, while the flow in the inflamed hand was greater than in the normal hand the difference was much less than in the case of infection. The contralateral vasoconstrictor reflexes from the normal to the inflamed hand were very slight in the case of the infected hand; of normal intensity in the case of gout. It is suggested that this indicates the existence of a relative vasoconstrictor block in bacterial inflammation in the interests of a permanently large flow of blood to combat the infection.

4. Temporary anemia of the hand (produced by bandaging) was followed by a moderate increase in the flow in a normal man.

5. In cases of congenital differences or differences originating in early life between the two hands, the blood-flow in the defective hand corresponded to its functional condition, being of normal magnitude when the power of the hand was good.

6. In a case in which some of the fingers of one hand had been lost by amputation, the flow per unit of volume was distinctly less in the defective than in the intact hand. This is mainly because the surface of the fingers is, in proportion to their bulk, so much greater than that of the rest of the hand. It is for the same reason that the flow per unit of volume is much greater in the distal half of the normal hand than in the hand as a whole.

7. In a case in which the innominate and the right common carotid arteries had been ligated one month previously, the flow in the right hand was two-sevenths of that in the left, although no pulse could be felt in the radial. Sixteen weeks later the ratio had risen to 1:1.3, the flow in the left hand being normal in amount.

BLOOD TRANSFUSION AND REGENERATION IN PERNICIOUS ANEMIA *

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A feature of much interest in the observation of cases of pernicious anemia is the behavior of the reticulated cells. In six cases of pernicious anemia, four of them treated by transfusion, which are here reported, this element of the blood-picture was studied with special care, and from these as well as from earlier cases of transfusion done in St. Luke's Hospital, certain conclusions are drawn in regard to the value of vital staining in cases of severe anemia, and concerning the subject of transfusion in general.

Ever since the discovery of the fact that by treating fresh, unfixed blood with solutions of various dyes, such as brilliant cresyl blue, polychrome methylene blue, neutral red, pyronin methylene green, etc., a curious and otherwise invisible structure could be demonstrated in the red cells, there has been much speculation as to its significance. Ehrlich, Pappenheim and Horsley were among the first to describe the phenomenon, but nearly all the subsequent studies have come from French and Italian laboratories (Hertz,[1] Ferrata and Boselli[2]). In suitably treated preparations this so-called granulo-filamentous or reticulo-filamentous substance appears in the form of coarse granular particles which are sometimes discrete, but more often occur in threads which frequently are woven into skeins or wreaths of great complexity and fill a considerable portion of the cells. In the blood of infants these reticulations are found in from 5 to 10 per cent. of the erythrocytes and in normal adult blood in from 0.5 to 2 per cent. In severe anemias, however, their number is much increased, running as high as 18 to 20 per cent., while in hemolytic jaundice, which is the condition par excellence for their prevalence, they may occur in still greater proportions.

Without taking the space at this time to enter into a discussion of the arguments pro and con of the various writers who have studied the matter, we may summarize briefly the views to which our own observations and a consideration of the literature have led us, by saying that the granulo-filamentous substance is not derived from the nucleus, is

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1. Hertz: Folia haematol., Arch., 1910, x, 419.
2. Ferrata and Boselli: Folia haematol., Arch., 1910, x, 451.

different from polychromatophilia and from the basophilic stippling seen in fixed preparations stained with panchromatic dyes, is not a preformed structure, but is a precipitation product of the stain, and is an evidence of youth in the cells and not of degeneration. In conditions in which a severe drain on the erythrocytes is being sustained by a well-functionating bone-marrow, large numbers of reticulated cells are found, whereas in aplastic cases they may be diminished almost to the point of absence, that is, in a manner somewhat comparable to the behavior of the erythroblasts the reticulated cells afford a direct insight into the hematopoietic activities of the bone-marrow. For clinical purposes they form a more convenient measure of this function than do the nucleated cells, as their percentage relations to the erythrocytes can be more easily and accurately determined, and their enumeration is to be urged as a part of the study of the blood in all cases of severe anemia. The relationship between the presence of the reticulated cells in the peripheral blood and the hemopoietic activity of the marrow was well illustrated in the case of a young man suffering from purpura hemorrhagica seen since the above was written. In spite of three transfusions of about 700 c.c., each done by direct intravenous injection, the red cells rapidly became reduced to 1,500,000, hemoglobin 25 per cent., while the leukocytes were 2,800, polynuclears 12 per cent. and lymphocytes 88 per cent., death resulting within two weeks of the onset of the symptoms. A highly significant feature was the total absence of reticulated cells, showing the complete inability of the bone-marrow to respond to stimulation.

The following technic for vital staining may be used:

TECHNIC FOR VITAL STAINING

Saturate 0.85 per cent. salt solution with brilliant cresyl blue. Filter this through a double paper to take out the excess of dye substance and to prevent precipitation on the slide. It is better to centrifugalize the stain before using it, in order to be sure that no undissolved particles remain in suspension. If any precipitate is present in the stain it will later be thrown down on centrifugalizing the mixed blood and stain and will cause confusion in counting the reticulated cells.

The following should be freshly prepared before use:

Saturated solution of brilliant cresyl blue in 0.85 per cent. salt solution.
Salt solution, 0.85 per cent. .....āā 5 c.c.
Sodium oxalate solution, 2 per cent. ..... 2 c.c.
Add the oxalate to the salt solution, then mix with the stain and filter.

Puncture the finger so as to get a free flow of blood, draw a good-sized drop into a red cell counting pipet, and using the stain as a diluent fill the diluting chamber. After thorough mixing, allow this to stand for ten minutes, then blow the contents of the mixing-chamber into a centrifuge tube and centrifugalize. Draw off the staining fluid with a capillary pipet, until only the sediment of cells remains. Draw the cells from the bottom of the centrifuge tube into a capillary pipet, then place a drop of these cells on the end of a clean slide which has been slightly warmed in a flame, and spread as in making ordinary blood-smears. The preparation will remain permanent indefinitely if mounted in neutral balsam or damar and not exposed to strong daylight.

In counting the cells the use of an Ehrlich eyepiece is of great assistance. A satisfactory substitute may be improvised, however, by cutting a hole about 8 mm. square in a disk of blackened cardboard and dropping this disk over the diaphragm of the ordinary eyepiece.

In the following cases of pernicious anemia, systematic determinations of the reticulated cells were made in connection with the study of the blood-picture by the usual methods, and as will be seen from the charts and the remarks in the clinical histories, an interesting relationship can be derived between the fluctuations of the red blood-cells and the curve of the reticulated cells.

The detailed histories of the cases are as follows:

REPORT OF CASES

CASE 1.—*History.*—M. M., a school teacher, aged 45 was admitted to the service of Dr. H. S. Patterson, Nov. 11, 1912. The chief complaints of the patient on admission were a feeling of weakness, dyspnea, palpitation of the heart and vomiting. About Jan. 1, 1912, she first noticed a feeling of languor and loss of appetite. In a short time the color of her skin and eyes alarmed her and she consulted a physician who treated her for "jaundice and weak kidneys." She was put to bed in February and remained there until April. For about a month she felt well and strong. In May she had palpitation of the heart on the least excitement and suffered from attacks of vertigo and morning headaches. Occasionally she had morning vomiting. From June to September she suffered from irregular short periods of colitis. She had been in bed for three months prior to admission, the most prominent symptoms being weakness, vomiting and anorexia.

Examination.—The patient is poorly nourished and acutely ill. Her complexion is pale and of a lemon-yellow tint. The sclerae have an icteroid tinge. The teeth and mouth are in good condition. The lungs are clear, the heart is of normal outline, the sounds are of good quality and are regular. There is a booming systolic murmur all over the precordium, which is loudest at the apex. There is no accentuation of the pulmonic or aortic sounds. The knee-jerks are absent. The blood-picture on admission shows red blood-cells 1,160,000; hemoglobin, 22 per cent.; white blood-cells, 5,000; polymorphonuclear leukocytes, 75 per cent.; lymphocytes, 25 per cent. The erythrocytes show marked poikilocytosis, anisocytosis, polychromatophilia and an occasional normoblast, but no megaloblasts. The rcticulated erythrocytes are only 0.5 per cent. of the total, showing that no active regeneration is going on. The Wassermann reaction is negative. The analysis of the stomach contents after a test-meal shows absence of free hydrochloric acid and a very low total acidity.

For two weeks the patient continued to grow worse, and the cell-count fell rapidly.

Treatment and Course.—December 5 her condition was so precarious that an immediate transfusion was decided on. A count made a few hours prior to the transfusion showed that the reticulated erythrocytes had risen to 8.2 per cent., and that there was an attempt on the part of the bone-marrow to produce new cells. The majority of the reticulated cells were macrocytes. The patient received only a small amount of blood at the time of transfusion, as the accompanying counts show. After remaining for from four to five days in a semicomatose condition, she began to improve rapidly. About a week after the transfusion sodium cacodylate grains ¾ daily subcutaneously was started. The rapid improvement which followed the transfusion seems to imply that the stimulating influence of the presence of the donor's blood was sufficient to arouse the patient's marrow into renewed activity. It also suggests that since with the small amount

of blood given in this case a favorable result was obtained, transfusion of a large amount of blood is by no means always necessary. The patient has improved steadily up to date. Although the blood-picture has returned practically to normal, the gastric achylia is still as pronounced as at first. It was subsequently learned that about six weeks after leaving the hospital this patient underwent a relapse. She was transfused twice more, but with little benefit, and early in July she died. A very interesting point is the sharp rise in the percentage of the reticulated cells preceding the rise in the erythrocyte count and the gradual fall of the percentage of the same cells as the total erythrocyte count became higher. As seen by Chart 1, the reticulated cells gradually fall to the percentage found in normal blood as the total count approaches its maximum.

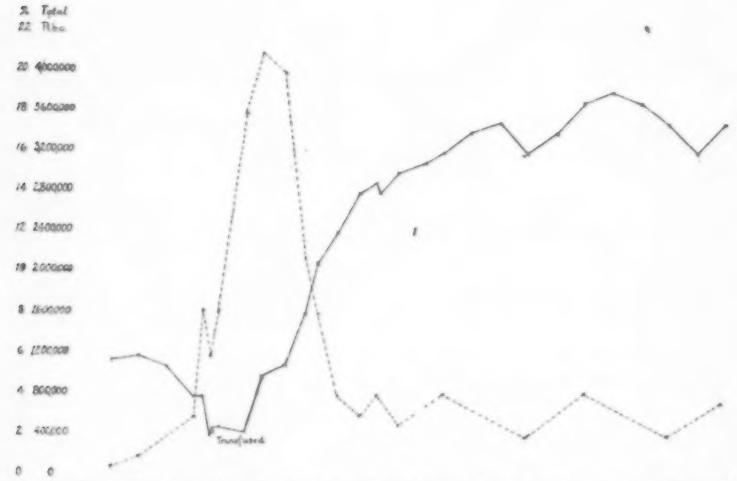


Chart 1.—Blood-findings in Case 1. In this and the following charts the solid line indicates the number of total erythocytes, and the dotted line the percentage of reticulated cells.

CASE 2.—*History.*—M. L., a housewife aged 52, was admitted to the service of Dr. S. W. Lambert, Dec. 12, 1912. Up to the time of the onset of the present illness the patient says she has been in perfect health. In February, 1912, after a short period of failing appetite, her attention was attracted to the sallowness of the skin and the yellowish tinge of her eyes. During the weeks following a general sense of lassitude developed, and with it attacks of vomiting, at irregular intervals. During the last six months she had noticed that the vomiting is less when she is quiet in bed than when up and about her work. In April she was in bed for one month for "nervous prostration." Subsequent to the rest she was able to resume her household duties with little physical discomfort besides shortness of breath and occasionaly numbness of the hands and feet. Six weeks before admission her weakness forced her to give up all work and go to bed. She has lost 37 pounds during the last year. The patient comes into the hospital "without a pain or an ache, but feeling miserably weak."

Examination.—The patient is pale, appears jaundiced and looks chronically ill. Her sclerae are distinctly yellow, and her left pupil is larger than the right. Her speech is slow and drawling. The teeth are in poor condition, with many missing. The lungs are clear. The heart is normal in size, but shows a faint systolic murmur, which can be heard all over the precordium, loudest at the apex

and pulmonic areas, and transmitted to the back and axilla. The analysis of the fasting stomach contents and also that of the test-meal shows achylia. The Wassermann reaction is doubtfully negative. The blood-picture is one of typical pernicious anemia. The morphology of the red cells shows poikilocytosis, anisocytosis, polychromatophilia and an occasional megaloblast and normoblast. The color index is 1.3.

Treatment and Course.—The patient could not be induced to take sufficient nourishment, declined steadily, and December 26 was transfused. The transfusion was very successful, both as regards the patient's immediate condition and the microscopical findings. The value of the microscope as a control in the operating-room during transfusion was demonstrated in this case. At the end of fifty minutes, when the surgeon was satisfied that the patient had received a large amount of blood, a red-cell count and hemoglobin determination showed that the amount received was almost negligible. A new anastomosis was made and in forty minutes the patient received a quantity sufficient to raise the total cell-count 1,000,000 per cubic centimeter. For a few days the patient was appreciably brighter, but the improvement was not long continued. For a month the total cell-count varied little. The vital staining of the erythrocytes showed plainly the presence of the donor's cells in the smears, for from the first

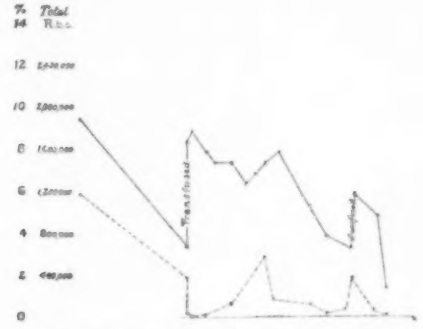


Chart 2.—Blood-findings in Case 2.

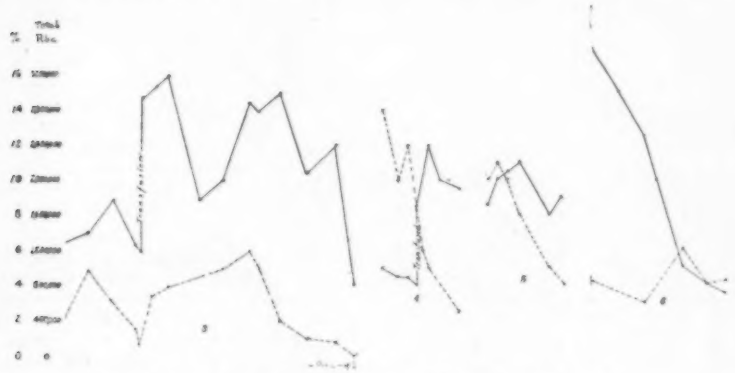
these did not take the stain as well as those of the recipient. From day to day they could be seen to have lost their hemoglobin to a greater and greater degree. After about two weeks they existed as shadow outlines of the original cells. At the end of three weeks a considerable number of these shadow cells were still present. There was no active regeneration on the part of the patient's marrow as far as could be determined by the blood-picture. The reticulated cells never reached more than 3 per cent. of the total (Chart 2) and megaloblasts and normoblasts were rarely seen. January 30 a second transfusion was done. While this time only one-half as many cells were given, the patient seemed toxic from immediately after the operation to the time of her death one week later.

Case 3.—*History.*—Dr. D., a Cuban physician aged 58, was admitted to the service of Dr. A. W. Hollis. In 1898 the patient was "executed" shortly before the beginning of the Spanish-American War. One bullet pierced the right shoulder and another passed through the body just above the trochanters as he fell. He was left for dead, but was later taken to the hospital in Havana, where he received treatment. Since that time he has had occasional attacks of diarrhea. During the last five years he has suffered from colitis, at irregular intervals and for periods of five to ten days, but has never regarded these as serious. Two years ago he was told that he had severe anemia. He was not incapacitated for

work, but during the last few months has lost much strength and weight. For the last two months the attacks of colitis have recurred with increasing frequency until the last two weeks, since when he has had from eight to ten stools a day, accompanied by much tenesmus. He vomits frequently and has morning headaches. His tendency to dyspnea and vertigo have necessitated his remaining in bed for the last two weeks.

Examination.—The patient is poorly nourished and shows signs of emaciation. The sclerae are yellow; the skin is pigmented. The mouth and teeth are in good condition. The lungs are clear. The heart is not enlarged, the sounds are weak and no murmurs are present. The abdomen shows general tenderness, especially over the region of the colon. The Wassermann reaction is negative, as is the blood-culture. The stomach contents show low free hydrochloric acid and low total acidity. The stools examined on several occasions always give positive tests for free blood. No parasites or ova are found.

Treatment and Course.—On admission the patient was acutely ill and much emaciated from his colitis. The colitis could not be checked after about three weeks' time; the weakness and vertigo were still prominent symptoms and transfusion was decided on.



Charts 3, 4, 5 and 6.—Blood-findings in Cases 3, 4, 5 and 6.

An artery-to-vein anastomosis was made and the blood allowed to flow for forty-five minutes. The total cell-count in the recipient was increased from 1,200,000 to 3,000,000 erythrocytes per cubic millimeter. The blood-picture before the transfusion had shown extreme poikilocytosis, anisocytosis, polychromatophilia and stippling of the erythrocytes. The immediate effect of the transfusion was apparent in the subsidence of the patient's symptoms with the exception of the colitis. This increased in severity for three or four days and then was checked. Much improvement followed for a month, the patient keeping the donor's cells and regenerating his own rapidly enough to keep the cell-count over 2,500,000. The "shadow cells" of the donor persisted for about three weeks in the blood-picture. The reticulated erythrocytes never amounted to over 6 per cent. of the total count (Chart 3). March 5 the patient on his own initiative was given salvarsan intravenously. The colitis at once again became severe, but in spite of this there was temporarily sufficient improvement to permit the patient to leave his bed. He insisted on a second dose of the salvarsan, but immediately after this the cell-count dropped and death followed in five days.

CASE 4.—*History.*—K. L., a German housewife, aged 46, admitted to the service of Dr. S. W. Lambert May 2, 1913. The patient complains of weakness and hemorrhage on entering the hospital. Her family and past histories are nega-

tive. She dates the onset of her present illness from the time about two years ago, when she suffered from "fever and chills" for several weeks. Since then she thinks that she has been losing weight and has gradually become weaker. About two months ago, at her regular menstrual period, the patient had a hemorrhage, during which she thinks she lost a large amount of blood. One month ago she discovered that she was unable to climb the stairs to her apartment because of weakness, shortness of breath and palpitation of the heart. During the last two weeks she has had three attacks of nosebleed. Six weeks ago the patient took some medicine which upset her stomach, and she has vomited almost daily since. She has numbness of the hands and feet. She is sure that she has lost 25 pounds in weight in the last year.

Examination.—The patient is a poorly nourished woman of middle life, who appears chronically ill. Her skin is of a deep lemon color and the mucous membranes are very pale. She is weak and prostrated. The sclerae have a slight icteroid tint. The mouth is in poor condition, containing many carious teeth. The tongue is moist and heavily coated. The lungs are clear. The heart is normal in outline. The sounds at the apex are regular and of fair muscular quality. The first sound is accompanied by a loud blowing systolic murmur, heard all over the precordium and transmitted to the axilla. The pulse suggests the Corrigan type. The patient's Wassermann is doubtfully positive and her blood-culture is negative. No gastric analysis was made because of her inability to retain food.

Treatment and Course.—Although there was no apparent change in the blood-picture during the first week of the patient's stay in the hospital, she grew rapidly weaker because of the inability to retain food. Over two-thirds of the nutrient enemata were expelled soon after they were given. May 10 she was transfused; the total cell-count after transfusion was 900,000 per cubic millimeter more than before. Before the transfusion the blood-picture had been one of active regeneration. The reticulated erythrocytes varied from 10 to 14 per cent. (Chart 4), and together with the presence of many normoblasts and megaloblasts showed that the bone-marrow was still actively functioning. The effects of the transfusion were transient. The following day found her in a stuporous condition, from which she did not rally. On May 19 she went into delirium, which was followed by coma and death in a few hours. As in the other cases the cells of the donor could after two or three days be distinguished from those of the recipient, and they persisted up to the time of the patient's death. In this instance the patient received what may have been an overwhelmingly large dose of blood, and it is possible that a smaller transfusion might have been more advantageous.

CASE 5.—*History.*—Mrs. L. S., a Swiss housewife, aged 42, admitted to the service of Dr. S. W. Lambert April 16, 1913, gives as her chief complaints general weakness and epistaxis. Eight years ago she was in the hospital complaining of a "goiter." After a few weeks in bed she was treated from the outpatient department of the hospital with "injections." She says that she then had "nervousness and a fluttering heart." These symptoms gradually disappeared and she was well until April, 1909. At that time she was treated in the hospital for pernicious anemia and was discharged with the diagnosis: pernicious anemia, acute thyroidism, chronic endocarditis. She was in the wards again in May, 1910, and April, 1911. Four weeks ago she was taken suddenly with a chill and fever. The doctor told her that she had "grip." When she attempted the resumption of her housework she found she did not have enough strength. Her face became puffy and her feet began to swell. She has been out of bed but one day since, and thinks that she has lost 12 pounds in the last month. The shortness of breath and palpitation of the heart have been growing worse. She has had several severe nose-bleeds in the last few days.

Examination.—The patient is a fairly nourished woman who appears chronically ill. The skin has an icteroid tint, and the face is slightly edematous. The sclerae are bluish-yellow. The teeth are carious and the mouth poorly kept. The lungs are clear. The outline of the heart is normal. Typical signs of mitral

BLOOD-COUNTS OF SIX PATIENTS WITH PERNICIOUS ANEMIA

Case	Date	Erythrocytes	Hemoglobin	Color Index	Leukocytes	Differential Count					Retic. Eryth. Per Cent.	Fragility / Hemolysis		Coag. Time*
						P.	L.	Eo.	Ba.	M.		Began Per Cent.	Complete Per Cent.	
1	11/11/12	1,160,000	22	0.95	5,000	75	25	..	..	..	0.5	0.40	0.34	2′ 20″
	11/18/12	1,200,000	20	0.83	4,600	83	16	1	..	..	1.0	....	....	2′ 15″
	11/25/12	1,100,000	20	0.90	4,000	78	20	1	1	..	...	....	....	....
	12/ 2/12	800,000	20	1.2	3,000	80	19	1	..	..	3.0	....	....	....
	12/ 4/12	800,000	20	1.2	....	..	..	..	..	..	8.2	....	....	....
	12/ 5/12†	400,000	12	1.5	.....	..	..	..	..	..	6.0	....	....	....
		500,000	12	1.2	....	..	..	..	..	..	...	....	....	....
	12/ 6/12	500,000	15	1.5	3,000	78	20	1	1	..	7.0	....	....	....
	12/13/12	480,000	15	1.5	6,000	60	40	..	..	..	8.2	....	....	....
	12/17/12	1,000,000	20	1.0	3,000	65	33	1	..	1	8.0	....	....	....
	12/23/12	1,100,000	35	1.6	5,000	82	18	..	..	..	18.0	....	....	....
	12/28/12	1,600,000	45	1.4	....	..	..	..	..	..	21.0	....	....	....
	12/31/12	2,100,000	50	1.2	6,000	70	29	..	1	..	20.0	....	....	....
	1/ 6/13	2,400,000	50	1.0	....	..	..	..	..	..	11.0	....	....	....
	1/11/13	2,800,000	50	0.9	6,200	68	31	1	..	..	8.0	....	....	....
	1/15/13	2,900,000	65	1.1	....	..	..	..	..	..	4.0	....	....	....
	1/16/13	2,800,000	65	1.1	....	..	..	..	..	..	3.0	....	....	....
	1/20/13	3,000,000	65	1.0	....	..	..	..	..	..	4.0	....	....	....
	1/27/13	3,100,000	67	1.0	6,000	74	25	1	..	..	2.5	....	....	....
	2/ 3/13	3,200,000	67	1.0	....	..	..	..	..	..	3.0	....	....	....
	2/10/13	3,400,000	70	1.0	7,200	70	28	2	..	..	...	....	....	....
	2/17/13	3,500,000	70	1.0	....	..	..	..	..	..	1.7	....	....	....
	2/24/13	3,200,000	72	1.1	6,800	57	43	..	..	..	...	....	....	....
	3/ 3/13	3,400,000	75	1.1	4,600	62	37	1	..	..	4.0	....	....	....
	3/10/13	3,700,000	77	1.0	....									
	3/17/13	3,800,000	77	1.0	....									
	3/24/13	3,700,000	80	1.0	5,000	67	31	1	1	..	1.8	....	....	....
	3/31/13	3,500,000	77	1.1	....									
	4/ 6/13	3,200,000	75	1.1	....	..	..	..	..	..	3.5	....	....	....
	4/13/13	3,500,000	..	...	....	..	..	..	..	..	2.1	....	....	....
2	12/14/12	1,900,000	50	1.3	4,800	75	23	1	1	..	6.0	0.42	0.38	2′ 26″
	12/26/12†	700,000	25	1.6	3,600	68	32	..	..	..	2.0	....	....	....
		1,700,000	45	1.2	....	..	..	..	..	..	0.8	....	....	....
	12/27/12	1,800,000	40	1.1	2,200	58	40	1	..	1	0.25	....	....	1′ 57″
	12/30/12	1,600,000	32	1.0	....	..	..	..	..	..	0.28	....	....	....
	1/ 1/13	1,500,000	30	1.0	3,000									
	1/ 3/13	1,500,000	35	1.1	3,500	76	23	1	..	..	0.76	....	....	....
	1/ 6/13	1,300,000	35	1.3	.....									
	1/ 8/13	1,400,000	35	1.2	....	..	..	..	..	..	3.0	....	....	....
	1/10/13	1,500,000	35	1.1	....	..	..	..	..	..	1.0	....	....	....
	1/13/13	1,600,000	32	1.0	3,600	72	28	..	..	..	0.8	....	....	....
	1/20/13	1,100,000	22	1.0	....	..	..	..	..	..	0.37	....	....	....
	1/24/13	800,000	20	1.2	2,300	33	64	2	1	..	0.25	....	....	....
	1/30/13†	700,000	18	1.3	....	..	..	..	..	..	0.45	....	....	....
		1,200,000	20	0.83	....	..	..	..	..	..	2.0	....	....	....
	2/ 5/13	1,000,000	20	1.0	3,600	42	57	1	..	..	0.5	....	....	....
	2/ 7/13	320,000	15	2.3	1,100	31	67	..	1	1	0.25	....	....	....

* By the Dale and Laidlaw method. (Jour. Path. and Bacteriol., 1912, xvi, 351.)
† Transfusion. ‡ Salvarsan.

BLOOD-COUNTS OF SIX PATIENTS WITH PERNICIOUS ANEMIA.—(Continued)

Case	Date	Erythrocytes	Hemoglobin	Color Index	Leukocytes	Differential Count					Retic. Eryth. Per Cent.	Fragility / Hemolysis		Coag. Time*
						P.	L.	Eo.	Ba.	M.		Began Per Cent.	Complete Per Cent.	
3	1/14/13	1,380,000	35	1.3	3,300	58	42	..	..	..	2.3	0.40	0.28	2′ 20″
	1/20/13	1,480,000	35	1.2	6,300	69	31	..	..	..	5.0	....	....	....
	1/27/13	1,800,000	40	1.1	4,900	59	40	1	..	..	3.3	....	....	....
	2/ 3/13	1,280,000	40	1.6	3,600	46	52	1	1	..	1.6	....	....	....
	2/ 4/13†	1,200,000	35	1.4	.....	..	..	..	..	..	0.9	....	....	....
		3,000,000	60	1.0	3,800	48	52	..	..	..	1.0	....	....	....
	2/ 7/13	3,100,000	60	0.96	3,600	52	46	1	..	1	3.5	....	....	....
	2/10/13	3,200,000	65	1.0	....	..	..	..	..	..	4.0	....	....	....
	2/18/13	1,600,000	48	1.5	6,000	64	33	3	..	..	...	....	....	....
	2/25/13	2,000,000	60	1.5	....	..	..	..	..	..	5.0	....	....	....
	3/ 3/13	2,900,000	70	1.2	4,500	62	37	1	..	..	6.0	....	....	....
	3/ 5/13‡	2,800,000	70	1.2	....	..	..	..	..	..	5.0	....	....	....
	3/11/13	3,000,000	75	1.2	....	..	..	..	..	..	2.0	....	....	....
	3/19/13	2,120,000	55	1.3	4,600	68	32	..	..	..	1.0	....	....	....
	3/24/13‡	2,400,000	60	1.2	....	..	..	..	..	..	0.76	....	....	3′ 15″
	3/29/13	890,000	25	1.3	1,300	28	68	4	..	..	?	....	....	....
4	4/ 2/13	1,000,000	20	0.9	10,000	48	50	2	..	..	14.0	0.40	0.30	2′ 59″
	4/ 6/13	900,000	25	1.2	5,000	50	47	3	..	..	10.0	....	....	....
	4/ 8/13	900,000	25	1.2	9,000	65	35	..	..	..	12.0	....	....	....
	4/10/13†	800,000	25	1.9	....									
		1,700,000	35	0.9	4,800	62	34	3	1	..	6.0	....	....	....
	4/13/13	2,400,000	50	0.9	4,500	58	41	..	..	..	5.0	....	....	....
	4/15/13	2,000,000	40	0.9	....									
	4/19/13	1,900,000	45	1.0	3,200	46	52	1	1	..	2.1	....	....	....
5	4/17/13	1,760,000	40	1.1	3,000	52	47	1	..	..	10.0	0.38	0.32	2′ 10″
	4/19/13	2,050,000	55	1.3	4,600	60	38	1	1	..	11.0	....	....	....
	4/21/13	2,100,000	55	1.3	4,200	64	34	2	..	..	10.0	....	....	....
	4/24/13	2,200,000	55	1.2	4,500	68	32	..	..	..	8.0	....	....	....
	5/ 2/13	1,600,000	45	1.4	....	..	..	..	..	..	5.0	....	....	....
	5/ 5/13	1,800,000	50	1.3	4,800	70	27	1	2	..	4.0	....	....	....
6	4/30/12	4,000,000	75	0.90	5,000	74	26	..	..	..	...	0.38	0.28	....
	5/17/12	3,600,000	60	0.83	4,500	60	38	1	1	..	...	....	....	....
	6/14/12	3,680,000	65	0.88	6,640	64	36	..	..	..	...	....	....	....
	7/18/12	3,700,000	72	0.97	2,100	70	30	..	..	..	...	....	....	....
	9/16/12	3,800,000	75	0.98	3,400	60	39	1	..	..	...	....	....	....
	10/ 3/12	3,500,000	65	0.92	4,200	58	41	1	..	..	...	....	....	....
	11/29/12	3,500,000	55	0.80	5,500	60	40	..	..	..	4.2	....	....	2′ 24″
	12/ 6/12	3,000,000	69	1.1	8,000	64	36	..	..	..	...	....	....	....
	12/13/12	2,500,000	75	1.5	5,800	66	32	..	2	..	3.0	....	....	....
	1/24/13	1,000,000	20	1.0	1,400	49	51	..	..	..	6.0	....	....	....
	1/30/13	800,000	15	1.0	3,500	51	48	1	..	..	4.0	....	....	....
	2/ 2/13	750,000	20	1.3	2,100	37	62	1	..	..	4.2	....	....	2′ 37″

stenosis and regurgitation are present. The right kidney is palpable on deep inspiration. Examination of a test-meal shows the absence of free hydrochloric acid, and a total acidity of 10; no blood or lactic acid. The Wassermann reaction is negative, as is the blood-culture.

This patient remained in the hospital for a little over two weeks. She was apparently comfortable and wanted to return to her own home and resume her housework. Although the reticulated erythrocytes were present in such large percentages and indicated an active marrow, there were surprisingly few nucleated red cells. The erythrocytic picture was typically that of pernicious anemia (Chart 5). The constancy of the red blood-cell count showed that the regeneration was taking care of the cell destruction. The resistance of the red blood-cells to hypotonic salt solutions was increased, for hemolysis did not begin until a dilution of 0.38 per cent. was reached, and to cause complete hemolysis a solution of 0.32 per cent. was required.

CASE 6.—*History.*—Miss C., a nursemaid, aged 43, was admitted to the service of Dr. S. W. Lambert. Beginning in September, 1911, the patient had a severe attack of diarrhea, which lasted six weeks. She had as many as fifteen movements a day. The stools contained both blood and mucus. Immediately following this she had palpitation of the heart on exertion, and was very nervous and easily excited. She was admitted to the hospital April 29, 1912, with a swelling on the front of the neck. She complained of loss of weight in spite of her good appetite. She also had marked polyuria. The superior thyroid arteries were ligatured, and while it was thought that there was improvement, the edema of the feet, nervousness, pain in the back and the weakness did not disappear. She remained in the medical wards from Sept. 16, 1912, to Dec. 21, 1912, having been transferred there from the surgical division. She was discharged on December 21 as improved. On Jan. 24, 1913, she was again admitted to the medical service, complaining of a "noise in the ears, nausea and weakness." Dyspnea was present on exertion, but no cough. For two weeks prior to admission she had been annoyed by a buzzing in the head that seemed to start in the ear and radiate toward the neck. She was very nervous, but had no sweating. The increasing weakness was becoming more and more noticeable.

Examination.—The patient is poorly nourished, acutely ill and looks "nervous." The skin is jaundiced. The eyes show slight exophthalmos, the sclerae have an icteroid tint, but the other eye-signs of Graves' disease are absent. There is a fulness in the thyroid region on palpation. A blowing systolic murmur is present in the gland. The lungs are clear. The heart is normal in outline, regular, forcible and rapid. All the signs of mitral regurgitation are present. Over the precordial area, and especially in the second left interspace, a to-and-fro friction rub is heard. There is edema of the lower extremities, especially on standing. In the right retina there were three fresh hemorrhages. The Wassermann reaction and two blood-cultures are negative.

Course.—The patient had constant fever, between 99 and 102 F. At first the diagnosis was somewhat in doubt; but a careful study of the blood showed that the anemia was of the pernicious type. The reticulated erythrocytes were never higher than 6 per cent. (Chart 6), and with the extreme degree of anemia the prognosis was considered bad. In this case also the resistance of the red blood-cells was increased and the coagulation time was much prolonged. The patient grew gradually weaker and died before a donor for transfusion could be obtained.

A summary of the findings in the six cases is given in the accompanying table.

GENERAL CONSIDERATIONS

It is unfortunately still true that any discussion of the treatment of pernicious anemia must be prefaced by the statement that the disease is

an incurable one, and that the instances in which complete recovery is alleged as having followed some particular method of treatment, are to be regarded as explicable either on the ground of faulty diagnosis or insufficient observation. Nor is this altogether astonishing in view of the vagueness of our notions concerning the real nature of the malady. In dealing with other, secondary, forms of anemia, the conditions are different, for we are able to train our therapeutic efforts in two directions, first, toward removing the underlying cause of the trouble, and, second, toward influencing the regenerative functions of the blood-forming tissues. In the case of pernicious anemia, however, our ignorance of its etiology converts all our attempts at causal therapy into the purest empiricism (leaving out of account the mooted cases of bothriocephalus, syphilitic and puerperal pernicious anemia), and impels us to the conclusion that for the present we shall accomplish most by endeavoring to stimulate the flagging hematopoietic energies of the bone-marrow.

Of the many measures having this object in view, transfusion of blood in one form or another seems to offer particularly promising possibilities, and the highly encouraging results reported by many clinicians (as for example, Bovaird,[3] Hürter,[4] Hansen,[5] Weber,[6] Morawitz,[7] Sachs,[8] Gulland and Goodall,[9] etc.) more than justify a wider application of the procedure.

Hürter believes in transfusing early and always recommends the operation just as soon as the blood-picture ceases to show evidence of active regeneration. Undoubtedly, some portions of the bone-marrow retain their functional capacity longer than others, but if the delay is too great these also lapse into a state of inertia from which they cannot be aroused, even by the penetrating stimulus of the hemopoietins in the transferred blood.

The history of transfusion is a long one, and those who are interested in its details will find them set forth in an excellent article on the subject by Werner Schultz,[10] which gives also a complete bibliography up to 1910. That it did not require the era of vascular surgery to popularize the measure, is shown by the fact that in 1875, Landois[11] was able to collect from the literature records of 347 transfusions from one human being to another. At about this period the same great physiologist, together

3. Bovaird: Med. Rec., 1911, lxxxi, 239.
4. Hürter: Med. Klin., 1911, Beiheft, No. 12.
5. Hansen: Verhandl. d. deutsch. Kong. f. inn. Med., 1911, p. 141.
6. Weber: Deutsch. Arch. f. klin. Med., 1909, xcvii, 165.
7. Morawitz: München. med. Wchnschr., 1907, liv, 767.
8. Sachs: Ztschr. f. Geburtsh. u. Gynäk., 1909, lxiv, 336.
9. Gulland and Goodall: The Blood, New York, E. B. Treat & Co., 1912, p. 133.
10. Schultz, Werner: In Grawitz: Klinische Pathologie des Blutes, Leipsic, 1911, p. 381.
11. Landois: Transfusion des Blutes, Leipsic, 1875.

with Ponfick,[12] Panum[13] and others, established the fact that transfusion with animal blood which previously had been widely resorted to, was dangerous, and that clinically only human blood could safely be used. Later the question arose as to whether whole blood or defibrinated blood should be employed, and this has been made the subject of extensive discussion and difference of opinion. Many of the German authors still prefer to inject defibrinated blood, regarding the greater ease of working with it as offsetting the danger of introducing the deleterious substances shown to be present by Köhler,[14] Edelberg,[15] Schultz[16] and others. Later work by Morawitz,[17] Fuld[18] and Moldovan[19] has proved that these hazards may largely be avoided by allowing the defibrinated blood to stand from one-half to one hour before injecting, for under these conditions the injurious bodies produced during the act of defibrination become altered into harmless modifications. Morawitz[7] and Schultz[16, 18, 20] were also able to show that the greatest danger to be provided against was the presence of untoward bodies of the nature of iso-agglutinins or iso-hemolysins in the two bloods, and that, therefore, no transfusion should be done unless the corpuscles and serum of the donor and recipient had first been tested reciprocally. In this connection it is worth nothing that Hopkins[21] has reported a case in which, although the cells of the donor were only slightly agglutinated by the recipient's serum, smears made immediately after the transfusion showed extensive destruction of the donor's cells by phagocytes from the recipient. Curtis and David[22] after experimental work on dogs do not consider defibrinated blood suitable for human transfusion, and Pike, Guthrie, and Stewart[23] have found that on standing a number of hours, defibrinated blood undergoes alterations affecting the corpuscles and impairing its nutritive and bactericidal qualities.

Further evidence of the changes occurring in defibrinated or clotted blood is offered by the work of Stevens and Lee,[24] O'Connor,[25] Brodie,[26] Sollmann,[27] and Stewart and Harvey[28] on the differences in the pressor

12. Ponfick: Virchows Arch. f. path. Anat., 1875, lxii, 273.
13. Panum: Virchows Arch. f. path. Anat., 1863, xxvii, 240.
14. Köhler: Inaug. Diss., Dorpat, 1877.
15. Edelberg: Arch. f. exper. Path., 1880, xii, 283.
16. Schultz: Deutsch. Arch. f. klin. Med., 1905, lxxxiv, 541.
17. Morawitz: Ergebn. d. Physiol., 1905, iv, 307.
18. Fuld: Zentralbl. f. Physiol., 1903, xvii, 529.
19. Moldovan: Deutsch. med. Wchnschr., 1010, xxxvi, 2422.
20. Schultz: Berl. klin. Wchnschr., 1910, xlvi, 1407.
21. Hopkins: THE ARCHIVES INT. MED., 1910, vi, 270.
22. Curtis and David: Surg., Gynec. and Obstet., 1912, xv, 476.
23. Pike, Guthrie and Stewart: Jour. Exper. Med., 1908, x, 371.
24. Stevens and Lee: Bull. Biol. Lab., Johns Hopkins Univ., 1884.
25. O'Connor: Arch. f. exper. Path., 1912, lxvii, 195.
26. Brodie: Jour. Physiol., 1900, xxvi, 48.
27. Sollmann: Am. Jour. Physiol., 1905, xiii, 291.
28. Stewart and Harvey: Jour. Exper. Med., 1912, xvi, 103.

substances in blood before and after defibrination or clotting. Clinical observation confirms this and various authors, such as Hürter, state that the therapeutic effects of whole blood are distinctly better than those following the use of defibrinated blood.

While the development of the art of vascular surgery to its present high degree, including as it does the possibility of transferring absolutely fresh and, as far as we know, unaltered blood from one individual to another, would appear to make all further consideration of the use of defibrinated blood unnecessary, it must be admitted that from the standpoint of the clinician, these surgical transfusions are still far from ideal. In spite of the various highly ingenious devices that have been suggested for facilitating the operation, it is usually time-consuming, except in the hands of particularly skilful operators, and is a considerable ordeal to both donor and recipient. This fact, together with the sacrifice of a vessel which is entailed, makes donors difficult to find and causes them to hesitate about serving a second time; but the most serious drawback lies in the difficulty of estimating the amount of blood transferred. Counting the recipient's cells and determining the amount of hemoglobin at regular intervals, during the transfusion, should never be omitted, but this is at best only a halting method of gauging the blood-flow.

Both our own observations and those of others lead to the conclusion that more is to be expected from small transfusions repeated at rather frequent intervals, than from a single one of large amount (Weber,[6] Henrot,[29] Hürter[4]). There is even a likelihood that, as in the case of other stimulants, unnecessarily large doses of blood may actually be injurious, and as it were, overwhelm the last flicker of regenerative activity still persisting in the marrow. Or, there is also the possibility that the abrupt change from a state of extreme blood-poverty to one in which there is a great profusion of vigorously functionating cells, by relieving the bone-marrow from the insistent demands to which it has long become habituated, allows it to subside into a condition of hopeless inactivity.

Several possibilities suggest themselves in explanation of the effect of the transfusion. Either the transferred blood is functionally active directly as a transplanted tissue, and its value, therefore, is proportionate to the length of time its elements remain intact, or it is conceivable that it may have an antitoxic action on the etiological factor of the disease. Turk,[30] for example, believes that the new blood, being less resistant than the patient's cells, combines with some putative hemolytic principle present, and so by temporarily protecting the bone-marrow, allows it

29. Henrot: Bull. de l'Acad. d. méd., Paris, 1913, lxxvi, 38.

30. Türk: Vorlesungen über klinische Hämatologie, Vienna, 1912, ii, part 2, p. 701.

opportunity to restore some of the lost cells. In the opinion of most authors, however, the transferred blood acts as a stimulant, especially to the blood-forming organs, and at least for a time, revives the power of blood regeneration.

Carnot[31] attempted to increase the effect of these stimulating bodies or hemopoietins by using blood from animals that shortly before had been subjected to a venesection, but while there seems to be some experimental basis for believing that this is possible, further work by Gibelli[32] and by Larrabee[33] has shown that the procedure offers little hope of being valuable clinically. The same thing is true of the efforts of Courmont and André,[34] and other French workers, to obtain increased stimulation of hematopoiesis by administering small doses of hemolytic serums. In this connection it is of interest to note that Walter[35] has reported a case of pernicious anemia treated effectively by repeated injections of blood taken from a patient with polycythemia.

Although, of course, it is perfectly possible and even probable that the benefit following transfusion is more or less a composite of all these factors, it seems most likely — and this opinion is shared by most writers on the subject — that it is the stimulation of the bone-marrow that is chiefly effective.

While the transferred cells may serve to tide over a more or less acute emergency, their life in the new host is certainly too short to account for the steady rise in red cells that is frequently observed during a considerable period following the transfusion, and it is hardly conceivable that this is merely the result of improved nutritional conditions. The persistence of the new cells has been variously estimated by different writers, but is generally supposed to be about three or four weeks. Our own observations, by means of the method of vital staining, incline us to the view that in most instances they do not last so long, two or three weeks being the usual period in our cases, and during the latter part of this time they are so poor in hemoglobin as to be of comparatively little functional value.

Although some clinicians (Esch,[36] Huber,[37] Mann[38]) have had good results from the subcutaneous or intramuscular injection of defibrinated blood, this has not been our experience, or that of the majority of writers. Both from our own observations and from a survey of the literature, the

31. Carnot: Folia haematol., 1909, vii, 75.
32. Gibelli: Arch. f. exper. Path. u. Pharmakol., 1911, lxv, 284.
33. Larrabee: Jour. Med. Res., 1911, xxiv, 345.
34. Courmont and André: Folia haematol., 1904, i, 389.
35. Walter: Med. Klin., 1911, vii, 728.
36. Esch: Deutsch. med. Wchnschr., 1911, xxxvii, 1943.
37. Huber: Deutsch. med. Wchnschr., 1910, xxxvi, 1077, and Verhandl. Deutsch. kong. f. inn. Med., 1910, xxvii, 147.
38. Mann: Wien. med. Wchnschr., 1911, lxi, 580.

conclusion seems justified that the optimum effect is to be expected from the repeated intravenous administration of rather small measured amounts of undefibrinated blood. The desideratum appears to be the employment of a method by means of which this can be effected with less difficulty for all concerned than is the case when a vascular anastomosis is undertaken, so that the measure may be made more easily applicable to the conditions of ordinary practice. Over twenty years ago von Ziemssen[39] reported numerous cases in which transfusion was successfully employed by such a method. It consisted in having one operator thrust a needle through the skin into the vein of the recipient, while another operator performed the same action on the donor. Three glass syringes of 25 c.c. capacity were kept constantly in action, one being filled with blood from the donor, the other being emptied into the vein of the recipient, while the third was being washed out with sterile salt solution by a third person before being again applied to the needle in the donor's vein. By this procedure von Ziemssen was able to transfer any desired amount of unaltered blood and to measure it accurately. Moritz,[40] in 1911, emphasized the advantages of the method and introduced some improvements in the technic which facilitated the puncture of the vein. Still more recently, Lindeman,[41] using the same principle, has devised a set of cannulas by the aid of which even small veins may easily be entered, and the danger of wounding the intima is reduced, and has reported thirty-six transfusions done without a mishap, one of them in a child of seven weeks.

CONCLUSIONS

1. The transfusion of physiologically unaltered blood is one of the most promising forms of palliative treatment available in pernicious anemia. The number of cases on record in which a remission of notable degree and considerable duration has followed immediately on a transfusion is so great as to make it impossible to regard these results merely as coincidences. If proper precautions are taken to select a healthy donor and by the usual tests for isohemolysins and isoagglutinins the serum and corpuscles of donor and recipient are found mutually congenial, there is no danger, and the measure should be employed earlier in the disease instead of waiting until the patient is in a desperate condition.

2. There is evidence in favor of the view that greater judgment and accuracy are needed in determining the amount of blood to be trans-

39. Von Ziemssen: Deutsch. Arch. f. klin. med., 1902, l, 491. Verhandl. d. Deutsch. kong. f. inn. Med., 1892; München. med. Wchnschr., 1894, xli, 349; 1895, xlii, 301.

40. Moritz: München. med. Wchnschr., 1911, lviii, 393.

41. Lindeman: Am. Jour. Dis. Child., 1913, vi, 28.

ferred. It is quite possible that too large an amount of transferred blood may be injurious, and that more benefit is to be expected from small doses introduced at intervals to be determined by the progress of the patient.

3. The enumeration of the reticulated cells by means of the method of vital staining affords a useful means of gauging the hemopoietic activity of the bone-marrow, and by watching the patient's progress in this way the indications for and effects of, various therapeutic measures can be well determined and supervised.

THE PATHOGENESIS OF THE CONTRACTED KIDNEY*

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In order to obtain a comprehensive insight into the pathogenesis of the various types of contracted kidney in man, it is first of all necessary to attack the problem from the experimental standpoint, and to attempt to produce in animals artificially the identical types of contracted kidney which are observed in human pathology. Unfortunately, up to the present time this has been possible only to an exceedingly limited extent. But in this regard certain pieces of work of the past year or two have served to advance our knowledge, amongst which that of my friend Ophüls in San Francisco, of my colleague Mackenzie in Toronto, of their pupil Dickson, and of Christian are especially worthy of mention.

On the other hand, more exact studies concerning the finer morphological structure of the kidney have appeared almost simultaneously in France and in Germany, and these undoubtedly must now form the essential basis for all experimental work. I have also occupied myself with similar studies for several years past, the results of which have in large part been published during the previous year by my pupil Suzuki. My lecture therefore logically resolves itself into three parts:

1. What is our knowledge concerning the morphological structure and the function of the normal kidney?

2. What particular structural elements of the kidney must be damaged to produce chronic contracted kidneys in animals?

3. What is our knowledge concerning the chief types of human contracted kidney?

I shall begin first of all with the question concerning the morphological structure of the renal tubules. As regards the construction of the renal tubular system, we have been accustomed to differentiate the following structural groups: The capsular epithelium, the convoluted tubules of the 1st order (the *"Hauptstücke"*), the Henle's loop, the convoluted tubules of the 2d order (the *"Schaltstücke"*) and the collecting tubules.

But if we are to take into consideration the newer histological studies and those founded on modern reconstruction technic — and I refer chiefly to those of Policard and Peter — we must elaborate the

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above classification still further. For Peter divides the ascending limb of Henle's loop into a lower cloudy and an upper transparent portion. He also calls that narrow tubule which unites the ascending limb of Henle's loop with the *Schaltstück*, and which usually lies adherent to the glomerular capsule at its hilus, the *Zwischenstück* or connecting piece. And, finally, he differentiates the primary collecting tubules from the main collecting tubules, as have some previous authors.

In contrast to this complicated composition of the more distal portions of the tubular system, the *Hauptstück* (tubulus contortus of the first order) has generally been considered in the literature as an absolute unit; or, at the very most, only the terminal end (the spiral piece of Schweigger-Seidel, *partie terminale* of Policard) was distinguished from the rest of the *Hauptstück*. Even Peter in his schemata of the renal structure in the various animals treats the *Hauptstück* as a single unit, only giving the terminal portion a special distinction in the cat. Indeed, we find exceedingly scanty information in the literature concerning the finer morphological differences which distinguish this terminal portion.

On the basis of the results obtained from a study of Altmann preparations and vital staining with carmin made in conjunction with Dr. Suzuki, I am now prepared to advise a still further division. For it could be easily determined that in all the animals studied (the rabbit, guinea-pig, rat, mouse, pigeon, to a certain extent also the cat and the hedgehog), the *Hauptstück* (convoluted tubule of the first order) can be divided into at least three parts and possibly four.

The first, or proximal portion, when stained by Altmann's method, is characterized by an extraordinarilly dense and deep staining rod-like structure. On the other hand, the second or middle portion is characterized by a much more diffuse and more delicate rod-like structure, whereas in the third or distal portion a gradually more and more marked solution into granules takes place, which become progressively more diffuse in distribution. This differentiation into three (or perhaps four) parts stands out still more distinctly in the carmin preparations, so that at first glance one can immediately tell which tubules in the cortex belong to the portions immediately efferent from the glomerulus and which represent the transition to the descending loop. In the rabbit one can still further divide the third or distal portion into a spiral and a straight part.

On the basis of these specific stains, I can only confirm the observation of Peter concerning the more compact arrangement of the tubular convolutions in the deeper glomerular levels, as compared with those lying nearer the surface of the organ. To my mind, the recognition of the characteristic structure of the terminal portion of the *Hauptstück* is

particularly important, for, as Peter has also pointed out, the fact that it runs deep into the medulla enables one to confuse it easily with the ascending limb of Henle's loop — a confusion which in certain recent works on vital staining has actually occurred.

Because of the fact that up to the present time the vital staining has been especially used in studying the secretory processes in the kidney, it seemed essential to know exactly where and in what manner the vital staining dyestuffs are excreted. From amongst the many dyestuffs that have previously been used, we have purposely chosen carmin, though for the sake of comparison we have also made use of trypanblue. It is, of course, impossible for me to give you the details of each of the exceedingly numerous varieties of experiments performed, nor is it possible at present to describe to you the historical development of this subject or the differences of opinion which still exist on important questions. I desire merely to mention that it was the work of Ribbert and of Arnold which above all others formed for us the starting point for further investigations.

One fact which I desire to emphasize most strongly is that the majority of the authors, though by no means all, have failed to make a sufficiently sharp distinction between the actual excretion of the dyestuff and the staining of the granules. This distinction is probably one of the most important contributions of our experiments. If the staining of the granules is taken as the index of the dyestuff excretion, then the excretion of carmin may be expected to reach its height twelve to twenty-four hours after the administration of the usual dose employed, for that is the time when a distinct staining of the granules in the cells is first to be observed. On the other hand, since it can be easily determined that only the epithelium of the *Hauptstücke* shows a granule staining, it seems self-evident that the excretion of the dyestuff takes place through just these cells and through no others. Incidentally, it must here be mentioned, that all observations which would seem to indicate that an excretion of carmin also occurs in the ascending limb of Henle's loop or in the *Schaltstücke* are based on an error. We should also prefer to believe that similar observations in regard to other dyestuffs such as toluidinblue, trypanblue, etc., are also due to false interpretation of the findings. What has been taken to be the ascending loop is nothing else than the distal portion of the *Hauptstück*. And in the *Schaltstück* or in yet more distant divisions of the tubular labyrinth, the dyestuff occurs intracellularly only, when for other reasons we have a right to assume that resorption has taken place.

Indeed, on the results of constantly repeated comparisons of Altmann preparations and carmin preparations from the same kidney, we assert that secretory granule staining occurs only in the epithelium of the *Hauptstück* and in the very beginning of the descending loop. The very

fact that the *Hauptstück* stands forth so conspicuously in the vitally stained preparations naturally indicates the possession of a special functional capacity for the excretion of dyestuffs. The variety of the observations in regard to the histological pictures observed during the process of carmin excretion is, in our opinion, to be explained by differences in the doses employed or in the duration of the experiment. If the carmin excretion be systematically followed at intervals of ten minutes, thirty minutes, one hour, etc., for several days or weeks, the following result is obtained. The intensity of the color of the urine and the repeated finding of numerous deeply stained casts of carmin in the collecting tubules of the kidney under observation, definitely indicate that the greater part of the dyestuff is excreted within the first half hour, or at most within the first hour after the injection. In microscopical preparations of kidney obtained after this time, the casts of carmin are either very scarce or entirely absent. Yet in this period when the chief secretion is taking place, no staining of the specific granules is to be seen, or at best only an extremely faint staining. Occasionally, when the dose administered is not too large, no morphological changes whatever are to be seen in the cells, which would indicate a carmin excretion. But if the carmin excretion is very marked, the picture which has been repeatedly described by A. Schmidt, Ribbert and others is to be seen; namely, pink staining of the brushlike marginal membrane (the *Bürstensaum*), together with an irregular granular precipitate at the base and on the surface of the brushlike margin itself.

The Altmann preparations show that in this period the specific rodlike or granular structure of the cells is unaltered. They demonstrate conclusively that the irregular granular deposit of carmin just described has absolutely nothing to do with the real cellular granules, but represents merely an increased concentration and precipitation within the brushlike marginal membrane which limits the cell interior from the lumen.

The carmin casts which are to be seen in the collecting tubules and occasionally also in the Henle loops present an entirely different appearance, consist of very much finer or coarser granules, and are always more or less uniform in size. The above mentioned facts all indicate that the dyestuff passes through the epithelial cells of the *Hauptstücke* in solution, and that only in the lumen of the more distal portions of the tubular system is it thrown down in granular form, due on the one hand to the slowing of the urinary current and on the other to resorptive processes. Here it is usually found embedded in albuminous material. Numerous authors, and more particularly Ribbert, have shown that a resorptive phenomenon probably takes place in the Henle loops, the *Schaltstücke* and to some extent also in the collecting tubules. But the final proof that it actually does take place is to be found in the fact that if the

experiment has lasted some length of time the epithelium of these tubules usually shows the presence of carmin granules, whereas in their lumina casts are still present. The irregularity of their distribution and their coarse appearance render it an easy matter to distinguish them from the secretory granule staining in the epithelium of the *Hauptstück*.

Although it now seems probable that during the main secretory period the excretion of carmin occurs in soluble form, the question must still be answered whether this excretion occurs exclusively through the epithelium of the *Hauptstück*, or whether it can also take place elsewhere as well, as, for example, through the glomeruli. As is well known, the occurrence of such a secretion through the glomeruli is at the present time denied. But in the mouse, if the carmin administration be pushed, carmin precipitate can even be encountered in the capsular space. Further, although all the epithelium of the *Hauptstücke* be severely damaged, as, for example, by chromium, a relatively rapid excretion of carmin will nevertheless still take place. The two facts speak for the assumption that the carmin is excreted in soluble form, not only through the epithelium of the *Hauptstück*, but also through the glomeruli, although probably in greater dilution. The fact that this excretion is ordinarily invisible does not speak against it, for if smaller doses are used the excretion can also take place through the epithelium without leaving behind any morphologically demonstrable traces.

We thereby assume a position to a certain extent opposing the present-day teaching, more especially as we desire to emphasize that the period of secretory activity must be sharply distinguished from the period of storing up—the *"Speicherungsphase."* According to our experience, the phase of secretory activity reaches its height within about one hour and then slowly diminishes, whereas the storing-up phase reaches its height only after twelve to twenty-four hours. From this alone one can conclude that the storing-up process is independent of the secretory process or of the intensity of the secretion. On the contrary, at that time when the cell is being most intensely perfused with the dye fluid, the granules are only very weakly stained, and then gradually the intensity of the staining increases in spite of the progressive diminution of the secretion. Nevertheless, it seems that the storing up of carmin is more or less dependent on a certain optimum rapidity of the intracellular perfusion. Increasing the rapidity of excretion by means of a diuretic immediately results in a prolongation of the period of storing up. Lowering its rapidity, as, for example, by lowering the blood-pressure, results similarly in a delaying of the storing-up process. A faulty staining of the granules by the vital stains may therefore be the result of either of two diametrically opposed functional disturbances, a hyperfunction or a hypofunction.

We, therefore, arrive at the conclusion that the vital staining of the granules in the renal epithelium has absolutely nothing to do with the actual secretion itself. The prolonged perfusion of the epithelial cells with the dyestuff merely offers the granules the possibility of storing it up. The intensity of the granule staining cannot, therefore, be used as an estimate of functional capacity, as has until now been done, or at best only with very careful reservations. I should like to emphasize that point most emphatically, for even in the most recent work the opinion has been repeatedly expressed that the intensity of the granule staining stands in direct proportional relationship to the functional capacity of the cells. In making such statements the normal physiological differences in intensity with which the dyestuff is stored up in the cell granules of the different divisions of the *Hauptstück* have, of course, been left entirely out of consideration.

On the other hand, the fact that the storing up of the vital stain occurs in definitely characteristic fashion in each of the different divisions of the *"Hauptstück,"* enables us to solve the important question whether the various renal poisons (cantharidin, arsenic, chromium, uranium, sublimate, etc.) damage the entire *"Hauptstück"* diffusely, or whether they possess a selective action on certain portions. Here again it is impossible for me to go into details. I desire merely to sum up the matter very briefly by saying that such a selective action does actually occur.

The various renal poisons permit a classification into three groups.

1. Those which damage mainly the terminal portion of the *Hauptstück,* but whose action may under the influence of larger doses also extend somewhat upward on to the middle division of the *Hauptstück.* Very rarely and only when extremely large doses are administered will the action extend on to the proximal division of the *Hauptstück* as well. To this group belong sublimate and cantharidin.

2. Those in which the damaged area is chiefly limited to the spiral portion of the distal division of the *Hauptstück,* spreading downward toward the Henle loops and upward on to the middle division, but rarely reaching as high as the proximal division. Characteristic of this group of poisons is uranium.

3. Those which primarily damage the proximal and middle divisions of the *Hauptstück,* though with larger doses spreading downward on the distal and transitional divisions. To this group belongs chiefly chromium.

I should not lay any stress on this specific localization of the action of the various renal poisons, were I not convinced that it possesses an important bearing on the analysis of the function of the kidney. It certainly cannot be an indifferent matter which of the three or four divisions is chiefly damaged by a certain poison, particularly as we know

absolutely nothing at present concerning what special functions each of these divisions may possess. In fact, on the basis of our numerous series of experiments on the artificial production of hydronephrosis, the injection of uric acid and the observation of physiological forms of epithelial pigmentation (H. Fischer), I believe we have the right to conclude that the various divisions differ from one another in regard to their excretory function.

In this regard I can to-day only refer you to the more detailed publication. I should merely like to mention that uric acid is mainly excreted in the first and second divisions of the *Hauptstück* and that the lipoid substances, as, for example, in diabetes, are similarly stored up in these divisions. On the other hand, Baehr of New York, when working in my institute, was able to demonstrate that in the diabetic kidney glycogen is not only stored up intracellularly, but also excreted specifically by the cells of the fourth or transitional divisions of the *Hauptstück*. The work proved that the glycogen deposition in the diabetic kidney is not an incidental degenerative process, situated, as has previously been thought, in the Henle loops. On the contrary, it is an important evidence of a specifically localized secretory process. Of especial interest is the fact, to which Baehr has also called attention, that cantharidin, which acts specifically on this fourth or transitional division, is able to render the kidney relatively impermeable to sugar.

The question concerning the differences in action of the poisons is made still more complicated by the fact that they not only pick out particular portions of the *Hauptstück*, but that they also produce different types of damage. For example, chromium, uranium and sublimate produce extensive epithelial necroses in the affected tubules, whereas cantharidin chiefly produces a very marked cellular swelling and vacuolization. And then, finally, even the necroses following the various poisons show differences, in that they may or may not be preceded by a stage of hyalin-droplet degeneration. These facts possess an important bearing on the formation of casts. For in poisonings with those substances which produce the cellular necroses, casts are present in large numbers, whereas in cantharidin and arsenic poisoning they are relatively infrequent. If it were true that cantharidin particularly damages the glomeruli, as most authors have assumed, then the formation of casts following its administration should, according to the teaching of Ribbert, be especially marked. In our numerous experiments with cantharidin we have practically never observed any damage to the glomeruli which was worthy of mention, or which could not similarly be observed following any of the other poisons. We cannot, therefore, agree with those authors who are of the opinion that a glomerulo-nephritis, or a specific damage to the glomerular capillaries of the renal vessels can be produced by the

use of cantharidin. Our experiments with arsenic have also led to a negative result in this regard.

The actual starting point of our researches along these lines was the work of Schlayer and Hedinger on toxic nephritis several years ago. On the basis of carefully planned experiments, these authors recommended a sharp distinction between vascular and tubular nephritis, which seemed to us to be worthy of a careful histological analysis. We were able to convince ourselves that, on the one hand, the topographical relationship of the damage effected by the different renal poisons employed by these authors was exceedingly varied and complicated; that, on the other hand, the histological picture following cantharidin poisoning showed that with far more justice it deserved to be classed as a tubular poison rather than a vascular, and that finally the great differences in blood-pressure which the authors themselves admit to be present in the tubular and the so-called vascular poisoning is more than sufficient to account for the existing differences in function. For these reasons, it seems to us that the division of the renal poisons into a tubular and a vascular group is not justifiable. We have been forced to the conclusion that all the poisons which we have studied act primarily on the parenchyma, and in fact on particular portions of the *Hauptstücke*. The variations in the functional disturbance produced by certain of the poisons can be better explained by differences in the topography of the area affected, and by the fact that the individual poisons have a different influence on the blood-pressure.

The knowledge that all the known renal poisons as at present administered act practically exclusively, in so far as is morphologically demonstrable, on the epithelium of the *Hauptstücke*, destroys all hope of producing experimentally by this means pathological pictures resembling the human nephropathies. Of course, contributions are accumulating in the literature which prove that if administered over a long enough period even these parenchymatous poisons may produce a contracted kidney. But for man it is, on the contrary, just the diseases of the glomeruli which form the most important etiological factor for contracted kidney. Sclerotic areas in the kidney have been produced by Ophüls with lead and with chromium, by Dickson with uranium, by Uyeno under Ponfick's direction with carbolic acid, and the question is still to be settled how these foci of sclerosis are to be explained. One author assumes a direct irritation to the connective tissue, the proliferation of which eventually compresses the epithelial elements. On the other hand, Uyeno and Ponfick believe that the damming up of the tubules by means of casts is the primary cause of the sclerotic areas; that the proliferation occurs in the vicinity of these obstructed tubules, and that this connective tissue increase by gradual contraction and compression causes the tubular shrinkage.

The pathological pictures which we obtained in chronic uranium poisoning thoroughly convinced us that neither of these two hypotheses represent the real causative factor, although it cannot be denied that the retention of casts is of some significance. The great majority of the casts, however, are flushed out of the organ in a relatively short time and only occasionally may some remain behind, become calcified and thereby incite a reactive inflammation in its vicinity which may lead to total obliteration of the lumen. We feel convinced that still another process plays the chief rôle. In accordance with the work of the most recent authors, amongst which that of Thorel, of Heinecke and of Tilp must be especially mentioned, we were able to observe the extraordinarily rapid epithelial regeneration in the damaged *Hauptstücke* in all animals, and could readily determine that this epithelialization had its point of origin primarily in the narrow limb of Henle's loop and in the remains of the lower transitional division of the *Hauptstück*. Should the advance of the proliferating epithelium be obstructed by impregnable necrotic masses, or the epithelium from which the regeneration ordinarily starts be too severely damaged, there then results a collapse, and, eventually, total destruction of that particular entire tubular system. The portion of the tubular system proximal to the point of obstruction undergoes a pressure and inactivity atrophy absolutely identical with that occurring in hydronephrosis. And in this manner the numerous atrophic islands in the renal cortex develop, which are particularly characterized by the fact that the glomerulus belonging to the atrophic focus is somewhat smaller than normal, but otherwise strikingly well preserved, that its capsule is thickened, and its capsular space dilated. Although the process I have just described leads to a tubular contracted kidney as distinguished from a glomerular, it nevertheless does in my opinion find its analogy in human pathology in the pyelonephritic contracted kidney, the uric acid kidney and the sclerotic foci proximal to renal cysts, etc.

But since the glomerular contracted kidney is, as a matter of fact, really the predominating type in human pathology, the most important problem was to find a means of producing a glomerulonephritis in animals. I have already mentioned that the glomerular lesions observed after the administration of the ordinary renal poisons can by no means be considered a genuine glomerulonephritis. Only in uranium nitrate poisoning have Christian and Mackenzie been able to observe certain changes in the glomerular loops which would seem to indicate a possible vulnerability of the glomeruli in regard to uranium.

Baehr has recently been studying these various problems in the Freiburg Institute in greater detail. By the subcutaneous, but above all by the intra-arterial administration of uranium, he has succeeded in producing experimentally absolutely typical pictures of human glomerulo-

nephritis, and especially of the Löhlein type of glomerular lesion occurring with chronic ulcerative thromboendocarditis. The process begins with blood platelet thrombi in the capillary loops, necroses of the endothelial capillary walls and exudation into the capsular space. Then follows absolutely characteristic proliferation of the epithelium of Bowman's capsule with the formation of typical epithelial crescents. And, finally, there result adhesions which lead to partial obliteration of the capsular space. Hemorrhages also accompany the glomerular changes, so that even macroscopically the characteristic red punctate dotting of the cortex is to be observed. Unfortunately thus far the animals have usually died within the first few weeks, so that no very far-advanced stage of contracted kidney has as yet been obtained. But Baehr has for the first time produced glomerulonephritis experimentally, and his researches are the first which point the way to the experimental production of glomerular contracted kidneys. Of particular interest is the fact that by similar intra-arterial injection of iodin, chromium and croton oil no such glomerular changes could be produced, so that uranium must possess a specific action.

Damage to the glomerular apparatus must by no means be considered as identical with damage to the renal vessels, as some authors have wrongly assumed, and there have also been attempts to injure only the vessels themselves. As I have already mentioned, it was especially Schlayer who believed that in cantharidin and arsenic he possessed poisons which specifically damage the renal vessels. But as Pearce, Hill and Eisenbrey have shown, an absolutely sharp distinction between vascular and tubular poisons cannot be made. Furthermore, a critical study of Schlayer's experiments, which Baehr has recently undertaken, has also shown that among other things the general circulatory disturbance produced by the so-called vascular poisons is one of the chief causes of the early oliguria and other functional changes on which this classification is based. We possess at present no means with which to damage the renal vessels alone, and, therefore, no means with which to induce in animals a reproduction of the vascular type of contracted kidney.

It must, therefore, be frankly recognized that up to the present time only tubular contracted kidneys have been experimentally produced in animals, but that on the basis of Baehr's experiments we can also expect to produce glomerular contracted kidneys in the near future. Only then will it be possible to study satisfactorily the effect of such renal changes on the general organism, and, what will interest the clinician most of all, their influence on the vascular system, on the heart, and on the adrenals.

For the time being we are, therefore, obliged to confine ourselves to the pathological findings in our human material. But even in human pathology there exists up to the present time such a confusion in terminology and in interpretation that a satisfactory understanding of kidney diseases is a very difficult matter. This is the reason for the oft-repeated complaint that we possess no clear and reliable classification of renal diseases, and that we make no sharp distinction between the actual inflammatory processes and the other pathological disturbances which affect the kidney. It was no less a man than Friedrich Müller who, at the Meran Congress of the *"Deutschen Naturforscher und Aerzte,"* distinctly advocated a division of the non-inflammatory from the inflammatory kidney affections under the names of the "Nephroses" and the "Nephritides," respectively. But the term nephrosis has not come into general use, and in order to preserve a terminology analogous to that for diseases of other organs, it would be better to replace it by the term "Nephropathy."[1]

Inasmuch as we know so very little concerning the etiological factors, it is permissible to classify the nephropathies on the basis of pathogenesis. We can best divide all diseased conditions of the kidney into those which are purely or mainly passive in nature, and those which are reactive or inflammatory in nature. The first group can be again divided into the disturbances in development and form, the disturbances in circulation and the metabolic disturbances; the second group, which is really a complicated mixture of passive and active processes, must also be arranged into subdivisions according to whether the inflammatory reaction chiefly limits itself to the blood-vessels and connective tissue, or to the glomerular apparatus or to the tubular apparatus with its own individual divisions.

Finally, according to the course of the pathological process, some of the subdivisions must be separated into the acute and the chronic affections. Although it is extremely tempting to compare for you the acute renal diseases with those facts which have been determined experimentally in animals, I nevertheless feel that I must confine myself to a brief sketch of the chronic renal affections, because, in default of material for satisfactory comparison in the field of experimental work, such a brief outline seems more necessary for a better understanding of the present-day conceptions. I have attempted to present a survey of the chronic renal affections alone, at the same time indicating the acute processes from which these develop. Although in the chronic affections of mainly passive origin — those of formative, degenerative or circulatory origin — the pathological condition under consideration usually develops

1. As used by me in 1909, and recently recommended by Barker (Am. Jour. Med. Sc., 1913, cxlv, 42).

insidiously from the very onset; the chronic affections of inflammatory origin are, on the contrary, usually ushered in by an acute process. The various forms of inflammatory contracted kidney result secondarily therefrom, and ought really to be considered as nothing more or less than cicatrices in various stages of development. In fact, the inflammatory contracted kidneys resemble the other chronic nephropathies of passive nature in this respect, for the reactive process is more or less completely extinguished and only a physical disproportion and perhaps a certain disturbance in functional equilibrium remains.

It is not my purpose to enter on a detailed description of these various chronic renal affections, referring you rather to the text-books of pathological anatomy in which the frequent and confused misunderstandings, as, for example, that in regard to chronic parenchymatous nephritis, have been subjected to a searching exposition in the light of recent investigations. But I desire to call your attention to one point, namely, the great variety which the several forms of contracted kidney present in regard to their pathogenesis, although they form only one subdivision of the chronic renal affections. I shall limit myself to a comparison of the genuine and the secondary contracted kidney.

THE CHRONIC NEPHROPATHIES

I. Nephropathies of *formative* origin (disturbances in development and form).

Examples: 1. Nephropathia cystica. Congenital cystic kidneys.
2. Nephropathia hydronephrotica. Hydronephrotic contracted kidneys.
3. Nephropathia carcinomatosa, etc. Carcinoma of the kidney, etc.

II. Nephropathies of *degenerative* origin (metabolic disturbances).

Examples: 1. Nephropathia diabetica. Glycogen excretion and deposition in the lowermost division of the "Haupstück" (convoluted tubule of first order).
2. Nephropathia urica. Uric acid collections in the resorbing portions of the renal tubules.
3. Nephropathia amyloidea. Amyloid degeneration of the capillary system.
4. Nephropathia Basedowiana. Fat infiltrations in the secretory portions of the renal tubules.

III. Nephropathies of *vascular* origin (circulatory disturbances).

Examples: 1. Nephropathia albuminurica orthostatica adolescentium.
2. Nephrosclerosis cyanotica. Kidney of passive congestion.
3. Nephrocirrhosis embolica. Embolic contracted kidney.
4. Nephrocirrhosis arteriosclerotica. Arteriosclerotic contracted kidney.
5. Nephrocirrhosis genuina. Genuine or primary contracted kidney. Granular atrophy. Presenile sclerosis affecting the smallest branches of the renal artery.

IV. Nephropathies of *inflammatory* origin.

Examples: 1. Nephrocirrhosis glomerularis. Glomerular or secondary contracted kidney. (The "chronic parenchymatous kidney" of older authors). Develops after an acute glomerulonephritis.
2. Nephrocirrhosis tubularis. Tubular contracted kidney. Develops after an acute tubular nephritis. Exceedingly rare in man, if it occurs at all. In animals it can be experimentally produced by chronic uranium poisoning, and by intra-arterial injection of iodin.
3. Nephrocirrhosis apostematica. Pyelonephritic contracted kidney. Develops after an acute suppurative inflammation of either hematogenous or urinogenic origin.
4. Nephrocirrhosis tuberculosa, etc. Tuberculous contracted kidneys, syphilitic, etc.

Even at the present day the idea is still widespread that the genuine or primary contracted kidney is the result of an inflammatory process, and the possibility cannot be denied that such a mode of origin may occasionally occur, as, for example, following the acute exudative lymphocytic or leukocytic nephritides of scarlet fever and of streptococcus infection, a possibility which even I myself have mentioned in my textbook. But it is now, as a matter of fact, beyond the shadow of a doubt that the majority of the uncomplicated cases develop as a result of a vascular disturbance, or, to be more exact, from a sclerosis of the finest branches of the renal artery, beginning relatively early in life and leading secondarily to the formation of atrophic foci in the parenchyma and to hyaline degeneration of the glomeruli, with a resultant focal inactivity atrophy of the tubules belonging to them. These facts, originally brought forward by Jores, have been thoroughly confirmed by Loehlein, Herxheimer, Fahr and Gaskell. This is, therefore, no primary disease of the filter apparatus; that is, of the glomeruli, but of the blood-vessels leading to the filter, a presenile arteriosclerosis of the finest branches of the renal artery.

The old teaching of Gull and Sutton concerning the arteriocapillary fibrosis in the "red contracted kidney" is herewith again brought to the front and properly honored. But, indeed, what induces primary disease of the smallest arterioles is still an unsolved problem. Is it only one manifestation of a general disease of all the smallest arteries (of the pancreas, retina, brain, etc.)? Or does it precede all the others and only secondarily, by reducing the volume of the afferent flow of blood to the renal filter, either reflexly or chemically call forth a constant high blood-pressure with its consequences, the classical cardiac hypertrophy and the sclerosis of the peripheral arterioles due to overwork and overuse? And if it does precede, to what is it then due? Is it the result of a congenital inferiority of the renal vascular apparatus, or is perhaps the filter relatively too small and its total diameter too narrow for the volume of its afferent blood-current? Is it perhaps due to some specific effect of

the ingested food or of endogenous irritants on the afferent blood-vessels of the renal filter? These are the problems which are still waiting for solution, as is also the question concerning the relation of the entire process to the chromaffin system. Only one thing seems certain, and that is that the renal sclerosis and contraction is primarily passive in nature, the result of the disease of the renal vessels. In this respect, this type of contract kidney approaches the arteriosclerotic, in which the disease, as one might say, spreads from the aorta outward into the individual branches of the renal artery and so only induces an inactivity atrophy of isolated, but larger areas of the kidney parenchyma.

Nevertheless, the amount of the filter which is incapacitated because of the peripheral disease of the renal vascular system in the genuine contracted kidney is far greater than that in the arteriosclerotic, and for this reason the latter does not induce such an outspoken secondary effect on the general vascular system and the heart. The larger the amount of filter, that is, of glomerular tissue functionally incapacitated, the greater must be the circulation through the remaining filter tissue in regard to blood-pressure and speed of the current, in order to keep up the amount of excretion necessary for the organism. This remaining filter tissue works on the borderline of its maximum functional capacity as long as its blood-supply is maintained at the proper speed and under a sufficiently high pressure. Hence, the normal output of urinary fluid and even polyuria. But it must be borne in mind, that although the kidney performs an increased work output, similar to that in cardiac hypertrophy, this always remains within definite limits and can, indeed, be chiefly increased by influencing the heart. This accounts for the relatively limited power of accommodation in the polyuric vascular contracted kidneys. Even the tubules that remain undamaged work more or less at their maximum. This interpretation of the process at least permits us to explain the frequent, and often very marked compensatory hypertrophy of the remaining glomeruli, as well as the remaining tubules, in such contracted kidneys.

The problem of the secondary contracted kidney is an entirely different matter; the primary factor is here an inflammatory change affecting the renal filter apparatus itself. The significance of this initial glomerular disease, attention to which had previously been called by Nauwerk, v. Kahlden, Ribbert, Reichel, etc., has recently again been particularly emphasized by Loehlein; and the subsequent studies of Gaskell, Baehr and others, have supplied ample confirmation of its importance. But these inflammatory contracted kidneys do not alone differ from the genuine vascular contracted kidneys in that the primary seat of the disease is in the glomeruli. One of their chief characteristics is usually the *general* involvement of the entire filter apparatus by the

pathological change, so that the reparative and the regenerative compensatory processes find much more difficulty in effecting a restoration of the normal function. For this reason the slightest overexertion, or even the physiological variations in renal work may very easily cause the renal tissue to quit work, thereby inducing uremia and the characteristic edema. The clinical picture is usually dominated by a glomerular oliguria, although if a sufficiently large part of the filter has recovered, this may give way to a polyuria. And this polyuria, exactly like that accompanying the genuine contracted kidney, depends on overwork of the remaining normal portions of the filter apparatus under the influence

TABLE SHOWING LOCALIZATION OF THE ACTION OF VARIOUS TOXIC AGENTS ON THE URINIFEROUS TUBULES OF THE RABBIT'S KIDNEY

Portions Generally Participating	Kind of Poison	Portions Participating to a Less Extent
Proximal Convoluted Tubule (Hauptstücke)	Chromium	
	Uranium	
Section 1.....	Cantharidin	
	Sublimate	
Section 2.....	↓ ↑	
	Uranium	Ascending limb of loop and intercalary piece.
Section 3.....	Cantharidin	
	Chromium	
	Uranium	
	Sublimate	Intercalary piece and ascending limb of loop.
Transitional Section.....	Cantharidin	Ascending limb of loop and intercalary piece.
	Chromium	
	Sublimate	

of an increased circulation through them, combined with an increased blood-pressure in the entire general vascular system. All our functional tests will actually test only these remaining normal portions of the filter apparatus which are working more or less at their maximum, and their particular vessels; but it must be remembered that they do not test the diseased tissue which is now in the scar stage.

Here in the secondary contracted kidney, the tubular secretory tissue connected with each diseased glomerulus is similarly put out of function, just as in the genuine contracted kidney, but usually to an even far more widespread extent.

The above considerations indicate that in the severe forms of nephritis oliguria depends on a glomerular disease and not on a disease of the

blood-vessels. Also the polyuria, both in the nephritic as well as in the vascular contracted kidney, in so far as the histological findings seem to indicate, does not depend on a hypersensitiveness of the still diseased vessels, but on the increased work of the undamaged vessels and their respective filter apparatus, or the only slightly damaged ones, or those which have entirely recovered from their damage.

These forms of polyuria, which I might term compensatory or accommodative in nature, must be sharply distinguished from the acute irritative polyurias of toxic origin. The latter depend on a local damage to the blood-vessel filter apparatus, the former on a functional accommodation, usually accompanied by simultaneous accommodative processes in the rest of the general vascular system.

I hope that with these few examples I have made it clear that the problem of acute nephritis is entirely different from that of the chronic nephropathies, just as in toxicology the problem of acute poisonings differs from that of the chronic. In the acute nephritides we have to do with the question of an acute damage to previously normal functions; in the chronic nephropathies the question is that of the possibilities for compensation and of a failure of these compensatory regulations. The opportunity to penetrate more deeply into these two problems and to bring forth the solution has now been made possible by the recent advances in our knowledge concerning the normal structure of the organ and the experimental production of tubular and glomerular contracted kidneys.

STUDIES ON URIC ACID OF BLOOD AND URINE, WITH SPECIAL REFERENCE TO THE INFLUENCE OF ATOPHAN *

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Until Folin devised his recent colorimetric method for quantitatively determining the uric acid of the blood, we were very much in the dark as to the actual amount of this substance in circulation. Abderhalden, in his text-book, states that the amount of uric acid in the blood is too minute for determination. The older methods, the cupric bisulphite method of Krüger and the silver nitrate method of Salkowski, are too crude and require too large an amount of blood for practical service. Folin hints that Garrod must have drawn considerably on his imagination in his *"Thread"* estimates, and expresses the opinion that practically all of the older statements in the literature as to the amount of uric acid in the blood, represent nothing more than guess-work.

This new method possesses two essentials: it is remarkably accurate and it requires comparatively small quantities of blood — from 15 to 25 grams.

Briefly, uric acid is precipitated from the mother liquor of a weighed amount of blood, and is again brought into solution in very small volume. The uric acid thus obtained is treated with Folin's phosphotungstic acid reagent and gives a beautiful blue color which can be compared in a colorimeter with a known standard uric acid solution. I have found the Autenreith-Königsberger colorimeter (in common use in the pthalein test of kidney function) admirably adapted to this purpose.

The accuracy of Folin's method can be tested by adding, as he has done, a weighed amount of uric acid to sheep's blood (which contains a negligible quantity of this substance) and then proceding as with human blood.

I

Folin's determinations of uric acid in the blood of unselected individuals on a mixed diet is the basis of the first accurate statements in this regard. His figures run from 0.7 mg. to 3.7 mg. of uric acid in 100 gm. of blood, the overwhelmingly larger number of cases giving values from 1.0 mg. to 2.0 mg.

I wish to report a number of estimations on the blood of unselected healthy individuals on a purin-free diet. I have also made similar

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determinations in unselected cases of various diseases. With one exception, to which attention will be called, the individual was kept on a purin-free diet at least three days before observations were begun.

TABLE 1.—URIC ACID ESTIMATION IN NORMAL INDIVIDUALS

	Mg. Uric Acid in 100 Gm. Blood		
J. C.	0.5	R. D.	1.3
H. D.	0.6	L. S.	1.4
M. D.	0.6	L. H.	1.7
A. B.	0.8	R. O.	2.1
R. C.	0.9	H. H.	2.5
H. D.	0.9	J. M.	2.5
J. G.	0.9	R. E.	2.9
S. M.	1.1		

Wide variations are seen in Table 1. The specimens of blood showing the smallest amounts of uric acid were taken from medical students leading rather sedentary lives. The three highest were from professional men; the highest from a very active civil engineer.

TABLE 2.—VARIATIONS IN URIC ACID IN A SINGLE INDIVIDUAL

Blood	24-Hour Urine			
Mg. of U.* in 100 Gm.	Amt. c.c.	U. Gm.	NH_3 Gm. N	N. Gm.
3/20 (Lost)	1,375	.44	.36	13.86
4/ 2 2.3	1,700	.34	.62	12.58
4/ 8 2.5	1,650	.29	...	9.02
5/21 2.4	1,410	.39	...	10.37
5/27 2.4	1,660	.31	.66	11.19

* U. in this and following tables means uric acid.

It has been known for a long time that while different individuals excrete in the twenty-four hours varying amounts of uric acid, such elimination for one and the same person is fairly constant. To ascertain whether the blood of a given individual on a purin free diet maintains at all times a constant uric acid content, the determinations of Table 2 were made. It appears here that while the uric acid of the urine varies to some extent, that of the blood is remarkably constant.

TABLE 3.—URIC ACID OF BLOOD IN DISEASE

	Mg. in 100 Gm. Blood		
Mitral lesion	0.5	Acute tuberculous pleurisy	1.7
Rheumatic fever	0.6	Chr. Interst. nephritis	1.8
Acute syphilis	0.8	Malaria	1.8
Chr. tuberculous pleurisy	0.8	Pneumonia	1.9
Pneumonia	1.2	Uremia	2.1
Pneumonia	1.3	Polycythemia	2.2
Sciatica	1.3	Graves' disease	2.5
Typhoid fever	1.4	Pneumonia	2.7
Ulcer of stomach	1.5	Gout	3.3
Pneumonia	1.6	Arterial hypertension	3.3
Amebic dysentery	1.6	Intermittent gastric supersecretion	3.7
Neurasthenia (?)	1.7	Gout	4.5

Determinations were made on the blood of a number of unselected patients suffering from various diseases. While rather wide variations in

Table 3 are seen, it is noted that gout, as has been pointed out by other observers, gives the highest values. Whether or not the patient showing the second highest amount of uric acid was a sufferer from the so-called gouty diathesis, is an interesting question. His disease has been called intermittent gastric supersecretion for want of a better diagnosis.

II

Much discussion has been devoted to atophan (2-phenylchinolin, 4-carbonic acid), a drug devised by Nicolaier and Dohrn, and claimed by them to markedly influence purin metabolism. Numerous uric acid determinations with reference to the influence of atophan on the urine have been made by other observers. All agree that this drug increases the uric acid of the urine. Various theories as to its manner of action have been expressed. Nicolaier and Dohrn believe that atophan influences, in some way, purin metabolism within the muscle and thus leads to increased formation and excretion of uric acid. So far as I know, no determinations of the blood uric acid, as influenced by atophan, have been made. The accompanying tables detail certain changes noted in the uric acid of the blood and urine in health and disease following the administration of atophan.

TABLE 4.—The Influence on Uric Acid in Blood and Urine of Atophan in Health

Date		Blood Mg. U. in 100 Gm.	Twenty-Four Hour Urine			
			Amt. c.c.	U. Gm.	NH_3 Gm. N.	N. Gm.
3/20	.....	...	1,375	.44	.36	13.86
3/21	A	...	2,240	.57	.42	.....
4/ 2	.....	2.3	1,700	.34	.62	14.04
4/ 3	.....	...	1,550	.35	.65	12.58
4/ 4	A.	1.6	2,450	.55	.73	14.03
4/ 8	.....	2.5	1,650	.29	...	9.02
4/10	A	2.1	2,333	.35	...	15.54
5/21	.....	2.4	1,410	.39	...	10.37
5/22	A	1.8	1,850	.72	...	13.20

In Table 4 the letter "A" indicates the day on which atophan was given. Two grams of the drug were administered in one dose and the blood obtained two hours later. Following the administration of atophan quite a drop in the uric acid of the blood occurs; simultaneously an increase in the total amount of urine with marked increase in its uric acid is seen. A slight increase in the ammonia and the total nitrogen of the urine also follows. The increase in the total nitrogen, however, does

not keep pace with the increase in the uric acid, and I think we are justified in concluding that atophan exerts a selective influence on the elimination of the latter.

TABLE 5.—Effect of Atophan on Exogenous Purins

Date	R. E.	Blood Mg. U. in 100 Gm.	Twenty-Four Hour Urine			
			Amt. c.c.	U. Gm.	NH_3 Gm. N.	N. Gm.
5/28	..... 7 a. m.	2.9	1,150	.46	.58	10.26
5/29	500 Gm. Thymus 2 p. m. Blood 7 a. m.	3.2	900	.66	.69	10.96
5/31	500 Gm. Thymus 9 a. m. Atophan 2 p. m. Blood	1.1	1,280	.75	.76	11.16

In the observations recorded in Table 5 the effect of atophan on exogenous purins is noted. It is seen that the same decrease in the uric acid of the blood, and increase in that of the urine, occurs, as well as the same changes in amount, ammonia and nitrogen of the urine as noted in Table 4.

TABLE 6.—The Influence of Atophan on Uric Acid and Urine in Disease

Date		Blood Mg. U. in 100 Gm.	Urine			
			Amt. c.c.	U. Gm.	NH_3 Gm. N.	N. Gm.
5/24	Sciatica	1.3	.....	...	...	.....
5/26	*A*, Sciatica.....	0.9	.....	...	...	.....
5/20	Intmt. gstr. superscrn..	3.7	880	.39	.74	6.77
5/23	*A*, Intmt. gastr. superscrn.	2.1	1,150	.41	.82	7.20
5/12	Aneurysm	1.0	.....	...	...	.....
5/14	*A*, Aneurysm	0.5	.....	...	...	.....
5/ 9	Chronic interst. nephr..	1.8	.....	...	...	.....
5/10	*A*, Chr. interst. nephr..	1.3	.....	...	...	.....
5/24	*A*, Cont.	1.5	.....	...	...	.....
6/ 4	*A*, Cont.	1.4	.....	...	...	.....
5/16	Gout	4.5	845	.32	.19	4.17
5/17	*A*, Gout	3.2	1,225	.46	.32	5.25
5/31	Gout	3.3	1,125	.33	.33	8.28
6/ 1	*A*, Gout	2.8	1,550	.42	.41	9.90
5/26	Graves' disease.....	2.5	1,300	.36	...	10.08
5/27	*A*, Graves' disease.....	1.6	750?	.33	...	8.40?

In Table 6 the effect of atophan on the uric acid of the blood and urine of patients suffering with various diseases is seen. Its influence seems to be the same as in health.

Clinically, the drug produces in gout very distinct amelioration of symptoms and decreases the size of the tophi. In other diseases, notably in one case of sciatica, in two of chronic arthritis and in two of acute rheumatic fever, no relief from pain or other amelioration of symptoms was noted.

TABLE 7.—Comparative Determinations of Uric Acid

Date	Blood Mg. U. in 100 Gm.	Time	Urine			
			Amt. c.c.	U. Gm.	NH_3 Gm. N.	N. Gm.
5/27	...	9 a. m.	(365)	(.058)	(.087)	(2.01)
5/28	2.4	9 a. m.	420	.072	.099	1.47
5/27	...	12 m.	(250)	(.075)	(.066)	(1.68)
5/28	1.2	12 m.	780	.234	.122	2.73
5/27	...	3 p. m.	(405)	(.048)	(.093)	(1.79)
5/28	0.7	3 p. m.	105	.058	.080	1.02
5/27	...	6 p. m.	(200)	(.065)	(.082)	(1.66)
5/28	0.6	6 p. m.	65	.010	.069	.82
5/28	...	6 a. m.	(440)	(.167)	(.236)	(5.05)
5/29	...	6 a. m.	310	.170	.287	5.33

Table 7 represents certain comparative determinations which were made at three-hour intervals. On a given day, starting at 6:00 a. m., with an empty bladder, the urine was collected at three-hour intervals until 6:00 p. m., and again at 6:00 a. m. the following day. The figures in parentheses represent the determinations made on these specimens. The next day the same procedure was followed, with certain additions; 3 gm. of atophan was given at 9 a. m., and blood for uric acid determinations was obtained at this hour and every three hours thereafter until 6 p. m.

As a result of the administration of three grams of atophan the following occurred:

In three hours (9 a. m. to 12 m.) the amount of uric acid in the blood was cut in half; the amount of urine passed during this period was treble that of the same period on the previous day, and the uric acid simultaneously eliminated was more than trebled; the ammonia was doubled and the total nitrogen almost doubled. In the next three hours (12 m. to 3 p. m.) the uric acid of the blood was again cut in half, but the total amount of urine passed was very small and the uric acid of the urine very little more than on the previous day. The ammonia and the nitrogen were less.

In the next three-hour period (3 p. m. to 6 p. m.) the amount of uric acid in the blood remains the same; unusual oliguria appears; the uric acid of the urine is remarkably low, the ammonia is reduced and the total nitrogen very much reduced.

It would thus appear from Table 7 that atophan stimulates the kidney to unusual activity and causes the rapid elimination of a large part of the blood uric acid. This stimulation seems to be followed by a reaction, in which a lessened amount of work is done by the kidney, the lowest ebb of its physiologic activity being reached about nine hours after the administration of the drug.

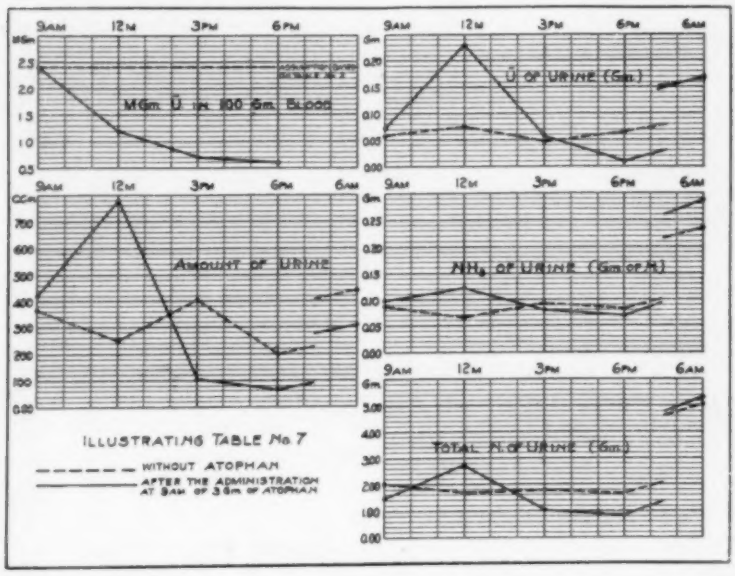

Chart showing comparative amounts of uric acid, NH_3 nitrogen and total nitrogen in blood and urine before and after the administration of atophan. Dotted curve, without atophan; solid line after administration of 3 gm. of the drug.

CONCLUSIONS

1. The amount of endogenous uric acid in the blood of different individuals varies widely; yet, for a single individual, this figure is a constant one.

2. (a) Atophan increases general renal activity; in addition, it exerts a selective stimulating influence on uric acid excretion. (b) It simultaneously reduces the uric acid of the blood. (c) Its influence over uric

acid metabolism would seem to be limited to its power of transferring, by means of the kidney, uric acid from the blood to the urine.

NOTE.—Since the above was submitted for publication, Folin and Lyman have detailed in the *Journal of Pharmacy and Therapeutics*, 1913, iv, No. 6, similar experiments. They reach like conclusions regarding atophan, i. e.: "The results obtained in this patient furnish a striking illustration of the fact that phenylquinolin carbonic acid acts on the kidneys (Weintraud) and does not mobilize (Brugsch) deposited urates."

Empire Building.

SOME FORMS OF URINARY NITROGEN AFFECTED BY THE ADMINISTRATION OF DESICCATED THYROID TO DEMENTIA PRAECOX PATIENTS *

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In a previous article, I showed that indol-acetic acid is frequently present in the urine of dementia praecox patients.[1] Later it was discovered that in the case of two dementia praecox patients the indol-acetic acid was endogenous and not derived directly from the tryptophan ingested.[2] Since there has been much discussion as to the relation of dementia praecox to the internal secretions and especially to that of the thyroid gland and since the administration of desiccated thyroid has given contradictory results as to its effect on nitrogen metabolism, it was thought worth while to determine the influence of the administration of thyroid primarily on the indol-acetic acid, and secondarily on the creatinin and total urinary nitrogen excretion.

PLAN OF TESTS

Four women patients, classified as cases of dementia praecox, were selected. They were all in apparently perfect physical condition. Their ages ranged from 29 to 32 years. Their approximate average weights were 94, 96, 115 and 101 pounds. During the test the patients were kept out of doors about six hours a day and were taken for a walk of nearly two miles daily.

The diet each day was constant in kind and quantity. Patients M. P. and M. O. B. received 6.3706 gm. of nitrogen daily during the first seven days of the test and 6.4995 gm. of nitrogen daily during the remainder of the time, in the form of coffee, milk, graham crackers, egg omelet and peanut butter. The daily diet of Patients G. G. and A. S. contained 9.2580 gm. of nitrogen and consisted of coffee, milk, graham crackers, a wheat breakfast food, ground meat and peanut butter.

The length of the feeding test was thirteen days. The second day the daily urine was collected and analyses begun. The eighth day a

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* From the Illinois State Psychopathic Institute.
* Submitted for publication Sept. 22, 1913.

1. Ross, Ellison L.: A Preliminary Note on the Excretion of Indol-Acetic Acid in the Urine, THE ARCHIVES INT. MED., 1913, xii, 112.

2. Ross, Ellison L.: The Source of Urinary Indol-Acetic Acid in Two Dementia Praecox Patients, THE ARCHIVES INT. MED., 1913, xii, 231.

5-grain tablet of desiccated thyroid was given each patient before each meal and this was continued for six days. The analyses were made before any of the urine was thirty-six hours old.

The Kjeldahl method was used for the total nitrogen determination, the Folin method for creatinin and my own method, slightly modified, for the indol-acetic acid. The method of determination of indol-acetic acid described in a previous paper[2] was modified, in that after adding the nitrite and hydrochloric acid, exactly three minutes were allowed to elapse before adding the amyl alcohol, and the shaking with the alcohol was shortened to one minute. The readings with the hemoglobinometer were begun exactly three minutes after the amyl alcohol was added.

The following Tables 1, 2, 3 and 4 give the results of analyses of the daily urines:

TABLE 1.—TOTAL URINARY NITROGEN EXCRETED PER DAY IN GRAMS

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First without	2.7945	3.9379	5.9840	7.8285
Second without	4.9784	2.9917	6.1840	8.0530
Third without	5.1973	6.3867	5.4540	14.3170
Fourth without	6.3867	6.7932	6.6881	.....
Fifth without	5.3606	7.0635	6.3662	9.0680
Sixth without	6.0861	7.5744	7.5580	7.7110
First with	6.7718	6.5612	5.6615	7.7330
Second with	5.4859	4.3622	7.5710	9.3080
Third with	6.4445	10.6415	7.8365	9.0190
Fourth with	6.4294	7.3188	7.7660	12.3050
Fifth with	10.8638	6.9152	7.7800	9.1690
Sixth with	5.2370	6.5549	6.4150	6.4260

TABLE 2.—CREATININ EXCRETED PER DAY IN GRAMS

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First without	0.3773	0.5918	0.5526	0.6801
Second without	0.6904	0.6046	0.6621	0.8892
Third without	0.7502	1.1097	0.7970	0.9788
Fourth without	0.8295	0.8532	0.8085	1.0480
Fifth without	0.6987	0.8826	0.6277	0.9668
Sixth without	0.7973	0.8664	0.6648	0.7778
First with	0.8413	0.7442	0.6528	1.0084
Second with	0.8466	0.5058	0.8564	0.9788
Third with	0.8562	1.2246	0.8599	1.0221
Fourth with	0.8223	0.7642	0.8108	0.8984
Fifth with	0.8850	0.8136	0.8100	0.8484
Sixth with	0.7320	0.8688	0.6102	0.8962

TABLE 3.—Indol-Acetic Acid Excreted per Day in Grams

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First without	0.0457	0.0550	0.1285	0.1912
Second without	0.1811	0.0606	0.1379	0.2291
Third without	0.2103	0.2875	0.1356	0.1888
Fourth without	0.2424	0.1968	0.1583	0.1962
Fifth without	0.1002	0.1603	0.2086	0.2528
Sixth without	0.1633	0.0662	0.1959	0.2361
First with	0.1838	0.0686	0.1382	0.5950
Second with	0.1372	0.0715	0.1550	0.2516
Third with	0.1997	0.1629	0.2125	0.2752
Fourth with	0.1548	0.1967	0.2631	0.2482
Fifth with	0.1723	0.1905	0.3533	0.3763
Sixth with	0.1442	0.2426	0.2489	0.4042

TABLE 4.—Weight of Patients in Pounds

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First without	....	....	115.00	100.75
Second without	....	....	114.00	100.75
Third without	94.50	96.52	115.00	100.75
Fourth without	....	....	114.75	100.50
Fifth without	94.25	96.00	114.00	100.50
Sixth without	....	....	114.00	100.25
First with	....	....	114.00	100.00
Second with	94.10	96.25	113.50	100.00
Third with	94.10	94.75	112.50	99.75
Fourth with	92.25	93.75	112.50	99.50
Fifth with	92.00	93.00	112.00	99.50
Sixth with	92.00	93.00	112.00	99.50

RESULTS OF TESTS

Due to the fact that the entire cooperation of the insane patients could not be obtained, a sharp division of the urine produced in one day from that produced during the following day could not be made. This in part explains the irregularity of the daily results observed in Tables 1 to 4. Since the irregularities of the daily results make it difficult to see any general increase or decrease in the outputs, the average daily results for periods of three and six days (Tables 5, 6 and 7) have been calculated.

TABLE 5.—AVERAGE DAILY TOTAL URINARY NITROGEN EXCRETED PER PERIOD IN GRAMS

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First three without.....	4.3234	4.4388	5.8740	10.0662
Second three without.....	5.9445	7.1437	6.8708	8.3895
Six without	5.1339	5.7612	6.3724	9.2278
First three with.....	6.2341	7.1883	7.0230	8.6866
Second three with.....	7.5101	6.9296	7.3203	9.3000
Six with	6.8721	7.0589	7.1716	8.9933

TABLE 6.—AVERAGE DAILY CREATININ EXCRETED PER PERIOD IN GRAMS

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First three without.....	0.6060	0.7687	0.6706	0.8493
Second three without....	0.7752	0.8674	0.7003	0.9309
Six without	0.6906	0.8180	0.6854	0.8901
First three with.....	0.8480	0.8249	0.7897	1.0031
Second three with.....	0.8131	0.8155	0.7437	0.8810
Six with	0.8304	0.8202	0.7667	0.9420

TABLE 7.—AVERAGE DAILY INDOL-ACETIC ACID EXCRETED IN GRAMS

Days With and Without Thyroid	M. P.	M. O. B.	G. G.	A. S.
First three without.....	0.1457	0.1344	0.1340	0.2030
Second three without.....	0.1690	0.1411	0.1876	0.2284
Six without	0.1572	0.1377	0.1608	0.2157
First three with.....	0.1736	0.1010	0.1686	0.3739
Second three with.....	0.1571	0.2099	0.2884	0.3429
Six with	0.1653	0.1555	0.2285	0.3584

DISCUSSION OF RESULTS OF TESTS

Even the results for the three-day periods do not follow a regular trend in all cases, as is shown by Tables 5, 6 and 7. Not in all cases do both three-day periods of the same six-day period agree. A general increase in the outgo of the urinary nitrogen, creatinin, and indol-acetic acid, however, is shown in all four cases with one exception in the case of A. S. as regards the total urinary nitrogen. This patient was peculiar also in that the absolute quantities excreted were much larger than those excreted by any of the other patients and the daily variations were especially large.

The averages for the thyroidless and the thyroid period show distinctly the same increase. Table 8 will make this point clear.

TABLE 8.—RATIO OF THE ELIMINATIONS DURING THE PERIOD WITHOUT THYROID (TAKEN AS 1) TO THOSE DURING THE PERIOD WITH THYROID

	M. P.	M. O. B.	G. G.	A. S.
Total urinary nitrogen....	1.338	1.225	1.125	0.974
Creatinin	1.202	1.002	1.118	1.058
Indol-acetic acid	1.051	1.129	1.421	1.662

These results on the total urinary nitrogen agree with those of a number of investigators. The increase of the elimination of creatinin resulting from the administration of thyroid agrees with the results obtained by Pfeiffer and W. Schulz.[3]

Table 4 shows the gradual loss of weight of all of the patients during the test. This, according to the observations of many, would be expected. In these instances, however, the loss of weight cannot be said, with any certainty, to be due to the thyroid alone. It may have been due, partially or wholly, to partial inanition. The daily intake of protein by each patient, calculated as usual, was in the case of Patients M. P. and M. O. B., 39.8 gm. during part of the time and 40.6 during the remainder. In Patients G. G. and A. S. it was 57.9 gm. These amounts are not considered sufficient by most authorities. They were all that these patients could be induced to eat regularly, however, the weather being hot and oppressive.

The protein intake in these cases has an important bearing on the interpretation of the results on urinary nitrogen, creatinin and indol-acetic acid. It is well known that during inanition the total urinary nitrogen and the endogenous nitrogen is decreased. If these patients were in a state of partial fasting, this alone would tend to decrease the total urinary nitrogen and endogenous nitrogen. Therefore there is a possibility that the thyroid has exerted a much stronger influence than is apparent.

CONCLUSIONS

The administration of desiccated thyroid to these four patients with dementia praecox caused: (1) an increase in the output of total urinary nitrogen; (2) an increase in the output of creatinin; (3) an increase in the output of indol-acetic acid.

3. Deutsch. Arch. f. klin Med., 1899, lxiii, 369.

MORPHOLOGY OF THE BLOOD IN EPIDEMIC PAROTITIS *

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Perhaps it is because of our general disregard of its importance as a disease that so little work has been done on the morphology of the blood in epidemic parotitis. From such a viewpoint it is true that a perfect knowledge of the pathological physiology of the disease is of comparative little import. But this disease, it has been observed, is accompanied by a lymphocytosis, and the problem of lymphocytosis is an interesting and important one. The blood-picture of this disease is also of distinct value in differential diagnosis.

A perusal of the literature on the blood-picture in this disease shows it to be very fragmentary; so that there is need for summarizing and a proper correlation of the results obtained by the various observers.

Since the work of Wile,[1] I have been unable to find any noteworthy contributions. Wile's bibliography refers to the work of Cabot,[2] who notes an absence of leukocytosis in this disease. Sasquépée[3] notes a slight leukocytosis, low polynuclears, increased mononuclears, a decreased eosinophil count and in complicating orchitis a leukocytosis. Krestnikow[4] records a lymphocytosis, mononuclear increase, and in complicating orchitis a polynuclear increase. Pick[5] found a leukopenia, increased mononuclears, decreased polynuclears and decreased eosinophils, in the orchitis a leukopenia. Turck[6] found a leukocytosis and eosinophilia. Wile found a lymphocytosis relative and absolute; eosinophils first lessened, later increased; polynuclears varying with the mononuclears. Complicating orchitis causing a tendency to polynuclear increase.

From these findings it appears that there is manifestly a lack of agreement among the observers as to what is the actual blood-picture. Some of the observers record a leukocytosis, while the others did not find it. A like difference of opinion exists with regard to the mononuclears and the eosinophils.

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* Submitted for publication Oct. 21, 1913.

1. Wile: Arch. Pediat., xxiii, 674.
2. Cabot: Clinical Examination of the Blood. (Ed. 5.)
3. Sacquépée: Arch. de méd. exper., 1902.
4. Krestnikow: Thèse de St. Petersburg, 1902.
5. Pick: Wien. klin. Rundschau, 1902.
6. Turck: Verhalten des Blutes bei acuten Infections-Krankheiten.

In this work, as in my work on pertussis,[7] I aimed to determine the successive changes in the leukocyte formula by studying the same cases throughout the disease, and after it had subsided, correlating these findings with the daily clinical notes.

MATERIALS

The eleven patients who come into this consideration were residents of the Industrial Home for Crippled Children, ranging in age from 9 to 20 years. Five of them were males.

Their general health had previously been good, and they were all free from such other disease activity at the time this epidemic appeared as might affect their cell counts.

PRECAUTIONS

The specimens were taken about an hour before meal time; thus avoiding a digestive leukocytosis. Another precaution was the counting of blood taken from both the lobe of the ear and the finger. On account of the proximity of the usual site for getting the specimens to the area of pathologic activity, it occurred to me that possibly the blood in such an hyperemic zone might be influenced more or less. But in a number of cases the blood-pictures were practically the same in both specimens.

METHOD

The first blood-count was made just as soon as the cases were suspected. At this time there was slight enlargement of the cervical and submaxillary lymph-nodes and perhaps a slight rise in temperature.

The second count was made on full development of the swelling, and the third when the temperature reached normal and the swelling was subsiding. Usually the temperature reached normal several days before the swelling subsided. After that, one or two counts were made at intervals of a week.

CONTROLS

It was impossible to get control counts prior to the onset of the disease, as there was no way of knowing who was exposed; but control counts were taken six months after the disease subsided when the children were in good health.

As a working formula for what should have been normal for these children, I assume that a leukocyte count of 8,000 and polynuclear of 72 per cent., lymphocytes 22 per cent., large mononuclears 3 per cent., transitionals 1 per cent., eosinophils 2 per cent., is about normal. If we count the lymphocytes and large mononuclears together, we have a mononuclear count of 25 per cent., and therefore 2,000 mononuclears to

7. Barach, Joseph H.: Morphology of the Blood in Pertussis, THE ARCHIVES INT. MED., 1908, i, 602.

the cubic millimeter. If a patient had 3,000 mononuclears, the figures read 50 per cent. increase and so on.

TOTAL LEUKOCYTE COUNTS

At the onset of the disease, when the patient is having mild constitutional symptoms and enlargement of submaxillary glands, but has not yet developed parotid swelling, the examination in two cases showed a leukopenia. One patient of 13 years showed a leukocyte count of 5,280 per c.mm., another of 20 years had 5,200 leukocytes.

During the height of the disease, when the parotid gland is swollen to its maximum, in the entire series the largest count was 7,800, the lowest was 4,000, the average being 5,700 per c.mm. This average is lower than my findings in a series of 150 cases of typhoid fever, in which leukopenia is one of the characteristic features. On studying the temperature charts and clinical notes in these cases I find that those which had the higher fever and greater parotid involvement showed the most marked leukopenia. In five cases in which the patients had most of the involvement on one side at the time of the examination, the count ranged between 6,100 and 7,800 per c.mm. In the remaining six, in whom both sides were equally large, and much larger than in the unilateral cases, the counts ranged between 5,000 and 5,680 per c.mm.

Leukocyte Count When Swelling Recedes.—By the time the parotid swelling was markedly diminished, which usually occurred between the fifth and seventh days of the disease, almost invariably the leukocyte count showed a cell increase.

Leukocyte Counts After Swelling Subsided.—In the counts made about a week after the swelling had subsided, the number of leukocytes seemed to vary, upward in half and down in the others. In the first half the leukocytes steadily increased toward the normal. In the others, their number oscillated.

Leukocyte Count Six months Later.—At this time when the children were all in their normal health, the leukocyte counts in every instance was considerably higher than during the activity of the disease. The average for the series being 7,920 per c.mm. as compared with 5,700 per c.mm. during the activity of the disease.

Polynuclears.—In not one case was there an absolute and relative increase of these cells throughout the attack. Two cases did show a relative increase in the early days of the disease.

In all cases as the parotitis subsided the polynuclears increased toward their normal number. Later counts showed irregularity as to the number of cells, but the counts were always higher than during the activity of the disease.

Mononuclears.—These were constantly above normal, except in two cases, which showed a decrease early in the disease.

The two exceptions behaved as follows: At the first three counts in one case there was a decrease in mononuclears of 5 per cent. to 2 per cent. and 10 per cent., while the three following counts showed an increase over normal of 33 per cent., 75 per cent. and 75 per cent.

In the second case, a young lady of 20, the mononuclears were decreased 25 per cent. and 5 per cent. at the first and second counts, but the third and fourth counts gave an increase of 5 per cent. and 30 per cent. in the mononuclears. These appear to be cases in which the blood reaction to the disease is delayed.

The Eosinophils.—Nearly all cases showed more of these cells after the disease had subsided than during its activity. But the total numbers and their proportions did not seem to present any definite course.

Other Cells.—Transitionals and mast-cells did not seem conspicuous in any of the counts. Nor did I notice any pathologic leukocytes, such as are occasionally found.

This series presented no opportunity for observing the effect of the complications of the disease on the blood formula.

SUMMARY

In uncomplicated cases of epidemic parotitis the leukocytes are affected in the following manner:

By the time the disease has manifested itself — even though the parotitis is not yet developed — a leukopenia is present. The number of lymphocytes is moderately increased and the polynuclears have fallen below normal. When the parotitis is fully developed there is a marked leukopenia, most marked in the cases with the higher temperature and greater parotid involvement. In this leukopenia the polynuclears are relatively and absolutely decreased, the mononuclears are relatively and absolutely increased.

As the disease subsides the total number of leukocytes, the polynuclears and mononuclears revert toward their normal proportion. The eosinophils, which are scarcely seen during the activity of the disease, are found in about their usual numbers as the blood returns toward the normal.

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A CLINICAL STUDY OF HYPERTENSIVE CARDIO-VASCULAR DISEASE*

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CONTENTS

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The study here reported was begun a year and a half ago. It was undertaken primarily with a view to determining whether or not a critical analysis of a large group of histories of persons with high blood-pressure would disclose any hitherto unsuspected relations between the symptoms or evidences obtained by objective examination and the subsequent course of the disease, on which a more exact prognosis might be based. The results of the study were reported[1] in part before the Section on Practice of Medicine of the American Medical Association in 1912. During the year that has elapsed since then it has been possible to obtain accurate information about a much larger proportion of this group of patients.

I. MATERIAL STUDIED

The material studied consists of the case histories of private patients examined by my father or myself during a period of approximately nine

* From the Department of Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York.

*Read before the Association of American Physicians, Washington, D. C., May 8, 1913.

* Submitted for publication, July 24, 1913.

1. Janeway, Theodore C.: A Study of the Causes of Death in 100 Patients with High Blood-Pressure, Jour. Am. Med. Assn., 1912, lix, 2106.

years, from the time when I began to make routine blood-pressure observations with the use of the wide armlet in 1903 until June, 1912. These histories are almost entirely the records of persons belonging to the well-to-do classes of society. A number have been observed personally over the whole period, but for the most part the information as to the subsequent history and the date and cause of death was obtained from the family physician originally referring the case or from his successor in charge of the patient. It is a pleasure to acknowledge the hearty cooperation received from many physicians throughout the country. Their careful answers to the inquiries made give this study much of its value.

An analysis of such a type of material has obvious defects as well as advantages. It is clear that the diagnoses of the causes of death, almost all unchecked by necropsy, have only such a degree of probability as one may expect from a group of general practitioners. This source of inaccuracy, however, was greatly minimized by the grouping which I adopted. On the question sheet sent to the physician I asked whether death had been by cardiac insufficiency, uremia, apoplexy, acute edema of the lungs, gradual anemia, pericarditis, by complicating acute infection or some unrelated disease, with a request for details. The weakness of a method of this kind is revealed by the fact that in only a single case, and that a patient seen by myself in his last illness, was pericarditis diagnosticated. For the investigation of pericarditis in patients with hypertension only a study of necropsy material is permissible. Of the other diagnoses, the majority are clinical rather than anatomical, and they may for the most part be accepted at their face value. Only in the discrimination between certain types of uremia and apoplexy is decision difficult. It is highly probable — and this was well brought out by Cabot's study of three thousand necropsies[2]— that apoplexy is the real cause of a certain number of deaths set down to uremia. In the consideration of my statistics, therefore, it must be assumed that the number of patients reported as dying of apoplexy is almost certainly below the true number, and that the total deaths credited to uremia contain the difference and are in excess of the facts. As in their other relations these two groups show many similarities, they can often be considered together, and the error then falls out of consideration. A small number of patients were said to have died "suddenly," without further details being given; no attempt has been made to classify these deaths further.

Questions were asked as to the existence or non-existence of certain clinical symptoms; these were an additional check on the diagnosis of the cause of death. The only statistical use which I have made of the information obtained from other physicians as to subsequent symptoms

2. Cabot, R. C.: Diagnostic Pitfalls Identified During a Study of 3,000 Autopsies, Jour. Am. Med. Assn., 1912, lix, 2295.

has been in the study of the incidence of hemiplegic attacks. The errors here will all be errors of omission.

For the purpose I had in view, it seems to me that the advantages of a study of such private patients far outweigh the defects. The facts most necessary were the first symptom and the prominent early symptoms exhibited by the patient. To obtain reliable information on these points requires both an intelligent patient and a physician experienced in taking histories with reference to the particular points involved. It is evident that the conditions were fulfilled from the side of the patient. So far as the other factor enters into the situation, the vast majority of the histories were taken by myself and the remainder by my father. The earlier ones are less complete in their information on some points than those taken after I had begun to make my case records with the definite object of their subsequent scientific utilization. Here, again, undoubted errors of omission exist, and it is probable that some of the symptoms of a minor nature are less completely represented than conspicuous symptoms such as severe dyspnea, anginal attacks or edema of the lungs. Apart from this, the omissions are probably fairly evenly distributed throughout the earlier histories and will not lead to substantial inaccuracies.

The physical examinations included in these statistics were also made by my father or myself. In this way, any errors due to the personal equation are practically a constant throughout all observations, and can thus be neglected. For a satisfactory study of prognosis, only such private material can be used. A study of symptoms from hospital records is so defective as to be of little value. In the first place, ward patients are largely unintelligent and unobservant, and early symptoms are apt to pass unnoticed. In the second place, hospital historians are inexperienced and vary greatly in their ability and the care with which they interrogate the patients. In this way, a series of records running over any considerable period of years would be uneven in character, the personal equation being a wholly unknown factor. Finally, it would be practically impossible in our hospitals to obtain more than a fraction of the subsequent information which I have been able to collect about these patients. If further argument is needed in defense of the use of such clinical material lacking necropsies, for a study the aim of which is chiefly prognosis, I cannot do better than to quote the first student of the hypertension problem, Richard Bright:[3]

> Another very important question is the length of time which this disease may exist in the constitution before it runs to its last final period: and although our experience in the hospital is great, the point of duration is yet undetermined; for, with all the advantages which an hospital affords for the multiplied accumula-

3. Bright, Richard: Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, Guy's Hosp. Rep., 1836, i, 338.

tion of facts, there are some points on which the information derived from its wards is defective and even apt to be erroneous; and among these may be reckoned one of great importance, the probable duration of life, under any disease. If a case is much relieved, the hospital physician loses sight of it, and in all probability sees it no more; knowing nothing of future relapses or of the ultimate result. On the other hand, a very large proportion of his cases are arrived at the most advanced stage of the respective disorders: the circumstances have been such as to render them inattentive to the earlier indications of disease; and it is only when they can no longer pursue their laborious occupations, that they are driven, too late, to seek relief. Hence the physician is liable to form a wrong estimate of the progress of the disease under more favorable circumstances; and it is necessary to correct his views by a comparison with the history and results of private practice.

There has not yet, perhaps, been sufficient time, since this disease of the kidneys first attracted attention, to say to what extent life may be prolonged while the body is under its influence; but I believe, with care, its fatal effects may be kept at bay, and a hazardous life may be protracted for many years. Should that care be neglected, the chance of life will be greatly diminished.

The total number of my case records for the nine years was 7,872. Of these, 870, or 11.1 per cent., showed at some time a systolic blood-pressure of 165 mm. Hg or over. I have chosen to consider only pressures above 160 mm., because there is now substantial unanimity of opinion that, taken with the wide arm band, such pressures are always pathological. The extensive life-insurance statistics of Woley and Fisher bear this out; I have always been convinced of it.[4] Cook[5] believes that 150 mm. will eventually prove the upper limit of normal systolic arterial pressure, and I am inclined to believe him right, when readings are made with care to exclude temporary factors. When patients are seen but once, one cannot be certain of this. Therefore, it is wise to exclude from consideration all patients who have not had a systolic blood-pressure of 165 mm. or over. In addition, systolic pressures as high as 165 or 170 mm. are not infrequent in patients with severe cardiac insufficiency, in exophthalmic goiter, and at times in aortic regurgitation, and are seen transiently without a satisfactory explanation. My total group of 870 patients includes a number of instances of what seemed to me temporary hypertension, not associated with the type of disease which is the subject of this paper. These cases were eliminated from consideration, and no attempt was made to obtain information about them.

While I have diastolic readings in practically all cases, they were by different criteria at different stages of the study, and are not strictly comparable with one another. In addition, the consideration of them would so much further complicate the large amount of statistical work embodied that I have omitted the diastolic pressure entirely from consideration.

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4. Janeway, Theodore C.: The Clinical Study of Blood-Pressure, New York. 1904.

5. Cook: Blood-Pressure in Prognosis, Med. Rec., New York, 1911, lxxx, 959.

Of the remaining cases, I was able to obtain definite information up to June, 1912, of 458. This group of 458 patients forms the basis of the statistical analysis which follows.

II. SEX DISTRIBUTION

The total group of 7,872 patients contained 4,660 men and 3,212 women; the percentages of men being 59.2 and of women 40.8, or 18.4 per cent. more men than women. This preponderance of men is probably largely dependent on the fact that neither my father nor I have ever engaged in obstetrical or gynecological practice. The group of 870 patients with high pressure contains 543 men (62.4 per cent.) and 327 women (37.6 per cent.), a preponderance of 24.8 per cent. for the men.

The group of 458 patients that I have considered as having had permanent hypertension was made up of 307 (67 per cent.) men and 151 (33 per cent.) women. The preponderance of men with high blood-pressure over women is, therefore, 34 per cent., as against 18.4 per cent. for all the patients observed during the nine-year period. Subtracting the latter figure from 34 per cent., leaves 15.6 per cent. as the apparent extra incidence of hypertensive disease in the male sex. Even taking the group of 870 patients who had at any time a blood-pressure of 165 mm. or more, the male preponderance by the same circulation is 6.4 per cent.

It seems clear, therefore, that the diseases associated with persistently high arterial pressure are decidedly more common in men than in women. In all the analyses, figures for the men and women have been tabulated separately and separate curves have been drawn for the two sexes.

III. PROPORTION OF LIVING AND DEAD

Of the 458 patients, 212 (46.3 per cent.) men and women had died by June, 1912; and 246 (53.7 per cent.) were living. Separating these by sexes, the figures are as given in Table 1.

TABLE 1.—458 PATIENTS WITH HIGH BLOOD-PRESSURE

		Living		Deceased		Preponderance
	Whole No.	No.	Per Cent.	No.	Per Cent.	Per Cent.
Men	307	144	46.9	163	53.1	6.2 deceased
Women	151	102	67.5	49	32.5	35.0 living
		246		216		
Difference			20.6		20.6	

This table brings out several striking facts: 1. The number of men who had died by the arbitrary date chosen for the completion of the statistics, June, 1912, was 6.2 per cent. in excess of the number still living. 2. For the women, the excess was 35 per cent. in the other direction; many more women were living than had died. In the same way it is seen that 20.6 per cent. more men than women had died during the same period.

It is hardly possible that accidental circumstances or differences in the distribution of men and women between earlier and later years of the nine-year period could account for so extreme a variation. I have always had the impression that the expectancy of life in women with arterial or renal disease was greater than in men. This analysis gives such impressions an objective foundation in fact. I am inclined to attribute this preponderance to the difference in mode of life, and especially in the demands made on men and women by their social environment in a group of such private patients. Women are far better able to shield themselves from influences leading to sudden rises of blood-pressure with the attendant danger of apoplexy and cardiac overstrain. In general, they can accommodate themselves more easily to the type of life best fitted to limit the progress of arterial and cardiac disease.

IV. AGE DISTRIBUTION

For 446 of the patients the ages were known. These ages, grouped by decades, are shown in graphic form in Chart 1.

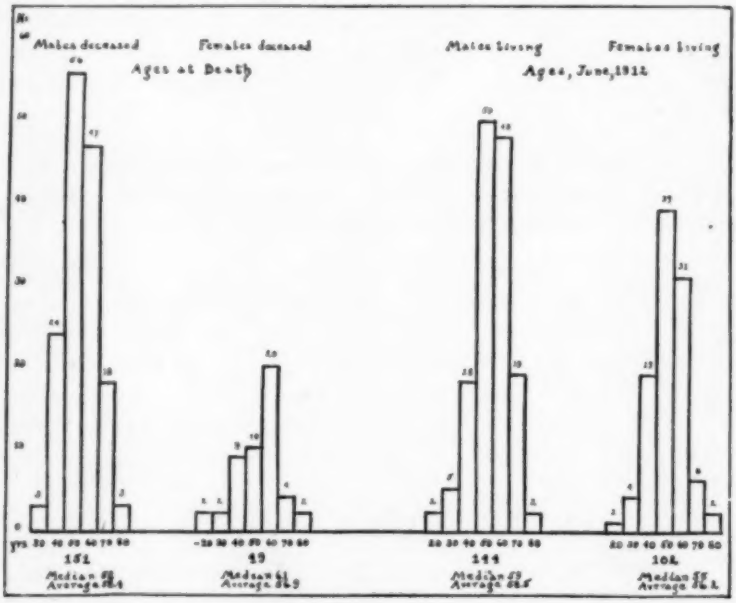

Chart 1.—Ages of 446 patients with blood-pressures of 165 mm. and over.

It is clear that the three decades from 40 to 69 years contain between 80 and 90 per cent. of all the cases. The exact proportions are given in Table 2.

TABLE 2.—AGES BETWEEN 40 AND 69 OF 446 PATIENTS, IN PERCENTAGES*

	Males	Females
Deceased	84.1	79.6
Living	80.6	87.3

* The percentages are computed on the basis of the totals in each case, that is, total number of deceased males, etc.

For every group, the next largest number of cases falls in the period of from 70 to 79 years. The number of patients over 80 is greater than the number below 30. This is, of course, in general conformity with all vital statistics: apoplexy, Bright's disease and heart disorders, under one of which categories these cases would be reported, show their greatest incidence above the fortieth year. On the other hand, these ages I believe are considerably higher than would be found in a similar number of patients with high blood-pressure dying in hospitals. Bright[6] tabulated the ages at death in seventy-four of his patients as given in Table 3.

TABLE 3.—BRIGHT'S CLASSIFICATION OF AGES AT DEATH OF 74 PATIENTS

Ages	Number	
8 years	1	
Under 30 years	19	
From 30 to 40 years	16	
From 40 to 50 years	21	51.4%
From 50 to 60 years	13	
Over 60 years	4	
	24	

The difference between the two sets of figures is very startling: 48.6 per cent. of his patients died before reaching the fortieth year. In commenting on these cases, Bright remarks:

> The youngest, whose age is given, is only 8; and there is one advanced to 73, showing, therefore, that neither youth nor age is exempt from this disease, but that it has cut off the greater part of its victims before the middle period has been attained.

Bright, of course, was dealing with cases of nephritis, acute or chronic, terminating fatally in a large London hospital. These patients did not all have hypertension, as is clear from his figures as to the proportion with hypertrophied hearts. They therefore represent some patients with the type of disease which I am considering, together with a group of the less chronic forms of nephritis. Even then, the very large proportion of persons under 40 years of age leads one to ask whether the disease from which all these young adults died has not become distinctly less common during the past seventy-five years, owing to changes in the hygiene and habits of the community. It is difficult for me to resist the impression that this is true.

6. Bright, Richard, Cases and Observations Illustrative of Renal Disease, Accompanied with the Secretion of Albuminous Urine, Guy's Hosp. Rep., 1836, i, 400.

I know of no published statistics with which mine are really comparable. Smith,[7] in 2,000 consecutive necropsies at the Massachusetts General Hospital, found 442 showing some arteriosclerosis. Of these, 21.3 per cent. were between 40 and 50 years of age, 29 per cent. between 50 and 60, and 25.8 per cent. between 60 and 70 — in all, 76.1 per cent. of the 442. The number of patients dying at 70 and over was double the number dying below 40 years of age. In my statistics, however, there were three times as many of the aged as of those dying before the fifth decade. The difference is mainly made up by the large number of patients in his group (19) with aneurysm, showing an average at death of 45 years, as against an average age of his cardiorenal group of nearly 55 years, of his cerebral group dying of apoplexy of 60 years, and of the patients dying of gangrene of 65 years. For the most part the aneurysm patients would not have shown hypertension during life.

I wish to call attention to the discrepancy between the average ages of the men and the women in my statistics, and the median for the ages of the two groups. There seems no question that the median is much more important than the average age from the point of view of prognosis; the median indicates a real tendency. From it, it is evident that the probability of living beyond 58 years for the men and 61 years for the women is as great as the probability of dying before that time. It also seems clear to me that, for a large proportion of these persons, the disease of which high blood-pressure was a symptom could not be looked on as materially shortening the span of life to which man has a traditional claim, but rather that it was for them an incident of growing old.

The difference of six years between the median for the women living and deceased is difficult to explain. It suggests the need for reserve in interpreting the high percentage of living women as evidence of a more favorable course of the disease in the female sex. Such ages at an arbitrary period in the course of a disease mean little in themselves. If it were possible to tabulate a sufficient series of cases terminating at or before a certain age, rather than patients living or dead at a particular date, much more definite conclusions would be warranted.

V. DISTRIBUTION BY HEIGHT OF SYSTOLIC BLOOD-PRESSURES

The study of the height of the blood-pressures has been the most disappointing part of this work. The blood-pressure naturally varies from day to day, from year to year. The only reliable figures that I could command were my own observations at the time of examination, sometimes one reading for a patient, sometimes many readings extending over a long period of years. I have in every case taken the highest recorded

7. Smith, William H.: Age in Its Relations to Arteriosclerosis and Death From Arteriosclerosis, Massachusetts General Hospital Report, 1908, ii, No. 1, 185.

Chart 2.—Blood-pressures (165 and over) of 458 patients.

systolic pressure, and have arranged these pressures in groups, in different ways, in the hope that some intelligible curve of tendency might be evident. The attempt at grouping at once showed what seems to be well known to statisticians, namely, the tendency of the mind to select the nearest multiple of ten when there is a choice between it and the five below or above. This I have found to be true in surveying my blood-pressure readings. For this reason, in the final groupings shown in Charts 2, 3 and 4, the readings have been redistributed to make groups at 20 mm. intervals of pressure from 160 up. Chart 2 shows the entire number of 458 patients thus grouped according to systolic blood-pressures, with the actual readings given in the columns.

It is evident that the lower pressures predominate in the living as compared with the dead groups, the median blood-pressure for the former being about 200 mm. and for the latter 220 mm. The same tendency is shown in Charts 3 and 4, in which the blood-pressure readings in relation to the number of cases are shown in the form of curves. It is of considerable interest to note in Chart 3 of the deceased patients that as many showed a blood-pressure of 220 mm. and higher as a lower figure, both men and women. Considered from any point of view, there seems to be no tendency for lower blood-pressures among the women than among the men. In fact, a much higher proportion of women, both living and dead, showed very high readings—280 mm. and over.

A tabulation of the duration of life as it was found for 197 of the deceased after my examination of the patient, arranged by blood-pressure readings, gives the figures shown in Table 4.

The patients dying in less than a year were for the most part seen during their terminal illness and are of little value for this study. The instructive groups are those that lived for six years and over; not a single one of these patients had a blood-pressure reading below 200 mm.

It does not seem to me that any very definite prognostic conclusions can be drawn from the height of the blood-pressure. I am confirmed in this opinion by certain individual cases in which extraordinarily high pressures were tolerated for six years and more, while other patients with very moderate elevation of pressure died in a much shorter time. While, therefore, the medians of the living and the deceased groups do seem to show a certain unfavorable significance of blood-pressures above 200 mm., I consider the height of the blood-pressure a minor factor in determining the expectancy of life.

VI. SYMPTOMS ASSOCIATED WITH HYPERTENSION

For many years I have interrogated patients with special care in the endeavor to determine the earliest symptoms associated with cardiovascular and renal disease. These patients so frequently seek medical aid for the first time when in the advanced stages of their malady, that it

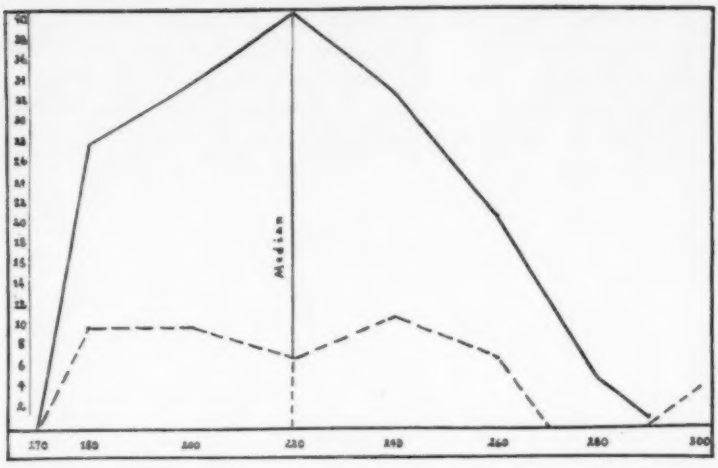

Chart 3.—Blood-pressure readings—deceased; solid line males, 163; broken line, females, 49; total, 212.

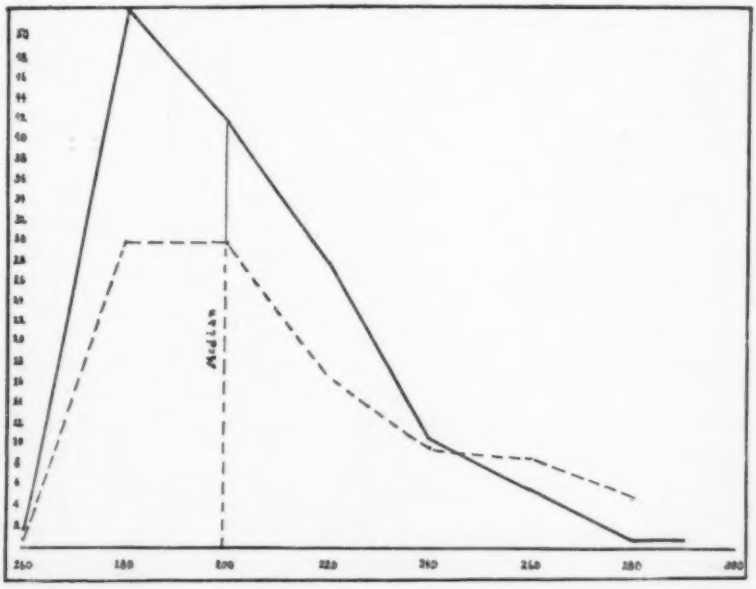

Chart 4.—Blood-pressure readings—living; solid line males, 144; broken line, females, 102; total, 246.

TABLE 4.—Duration of Life of 197 Deceased Patients After Examination and Finding of High Blood-Pressure

Duration	Systolic Blood-Pressure Readings in Millimeters														
	165 to 170	175 to 180	185 to 190	195 to 200	205 to 210	215 to 220	225 to 230	235 to 240	245 to 250	255 to 260	265 to 270	275 to 280	285 to 290	295 to 300	Totals
Less than 1 year.....	1	17	9	10	7	15	13	12	8	3	2	2	0	1	100
1 year.....	3	5	5	4	3	5	0	7	6	1	1	0	0	1	41
2 years.....	0	2	1	3	0	3	1	3	2	1	0	0	0	0	16
3 years.....	0	4	3	1	2	0	2	1	1	1	0	0	1	0	16
4 years.....	0	1	3	3	1	2	0	1	0	2	0	0	0	1	14
5 years.....	0	0	0	0	0	1	1	2	0	0	0	0	1	0	5
6 years and over..	0	0	0	0	1	1	0	2	0	0	0	0	0	1	5
Totals	4	29	21	21	14	27	17	28	17	8	3	2	2	4	197

has seemed to me of particular importance, in dealing with an intelligent group of patients, to trace back as far as possible to the first deviation from accustomed health. In many instances the task is impossible, because of preceding disease of some other nature, during which the hypertensive cardiovascular disease has developed as a sequel or concomitant. This is particularly true of diabetes in elderly subjects. With careful study, however, one may often find definite symptoms of failing cardiac reserve force, of urinary disturbance, of circulatory brain disorder, or a still less definite sense of fatigue, remembered as originating years before the physician was consulted. A knowledge of these early symptoms is so important for the recognition of the existence of serious organic disease that I feel justified in enumerating the symptoms that have appeared in this group of patients. They group themselves naturally into certain categories.

1. Cardiac Symptoms.—The most important numerically are the cardiac symptoms. Dyspnea stands first, beginning either with some shortness of breath on exertion or a paroxysm apparently coming out of a clear sky. The severest grade, of course, is seen in connection with the somewhat rare attacks of acute pulmonary edema. Anginoid pain on exertion has been characteristic of a considerable number of patients. Some have had purely subjective cardiac disturbances, palpitation or extrasystoles, of which they were unpleasantly aware, less often other arhythmias. Some had paroxysmal tachycardia for years before death. Edema of the legs, while a common late symptom, frequently appeared early, and in two patients was the initial symptom.

2. Renal Symptoms.—Polyuria, nocturia or frequency of urination were admitted by a very large number of patients. In many cases it was not possible to determine whether nocturnal frequency indicated nocturnal polyuria or not. The elderly men with hypertrophied prostates naturally complained of nocturia, and it was not possible in them to determine from their story when polyuria was superadded. The symptom is, I believe, of great importance, especially marked degrees of polyuria. In the subsequent tabulation it has been necessary to group all those complaining of nocturnal frequency in the same category, though it is fairly certain that in a number this symptom must have been due to local causes. The significance of the symptom will, therefore, be higher than actually appears from my tabulation. Oliguria was practically impossible to determine from the patient's statement. Albumin and casts were discovered incidentally as the first evidence of disease in twelve of the deceased men and in no women. This illustrates well the advantage of life-insurance examination for the early detection of chronic disease.

The striking absence of onset with general edema of nephritic type indicates, as clearly as anything, the wide divergence of these patients

from patients with high blood-pressure as found in hospital wards. I believe, however, that were the histories of our hospital patients taken with the same degree of care, some symptoms would be found antedating the onset of general anasarca in almost all cases.

3. Cerebral Symptoms.—Cerebral symptoms were noted early by many patients. Headache was the most frequent. The study of significance of headache has been beset with many complications, for a surprisingly large number of these patients have been subject to migraine throughout life. Some patients have been able to name a definite date when the character of the headache changed completely; others have noted a greater severity of the paroxysms. In still others, headache has appeared for the first time with the onset of the vascular disease. So commonly have patients described to me a particular kind of headache that I have almost come to look on it as a typical nephritic or hypertensive symptom. This headache is one which appears on awakening, or wakes the patient during the early morning hours, has its greatest intensity before arising, and passes away either immediately after breakfast or during the course of the morning, to reappear in the same manner day after day for considerable periods. The intensity of the pain and its location have varied somewhat, the most severe being similar to bad migraine, and in a few cases it is attended by nausea and vomiting. The time of onset and offset has been the characteristic of greatest constancy. Throbbing has accompanied it in some cases, but not in all. I shall refer to this type hereafter as "typical" headache. Sensations of fulness or pressure in the head have been noted by many patients who did not suffer from actual headache.

The following case histories illustrate this type of headache and are of particular interest:

CASE 44.—Male, designer, aged 45. Father died of Bright's disease, mother of apoplexy. Consulted Dr. E. G. Janeway on Feb. 23, 1905, because of headaches for ten years. The headache regularly began in the morning on arising and lasted until noon. It was occipital and radiated to the vortex. During the past one and one-half years the patient had lost 35 pounds in weight. For a year he had had transient attacks of aphasia and for two months had risen once at night to urinate. He had no cardiac symptoms whatever. On physical examination he showed slight cardiac hypertrophy, extreme accentuation of the aortic second sound, moderate peripheral arteriosclerosis and a blood-pressure of 255 systolic, 170 diastolic. The reflexes were generally increased, with a slight ankle-clonus on the right. The urine was 2,160 c.c., specific gravity 1.015, with a moderate amount of albumin, and at times a few hyaline and granular casts. The patient died in October, 1906; the cause of death could not be determined.

CASE 41.—Brother of the preceding, piano-tuner, aged 37. Consulted Dr. E. G. Janeway on April 7, 1908, because of headaches. For seven or eight years he had been subject to occasional occipital headaches. For three months the headache had come daily, beginning in the occipital region and radiating forward to the frontal region. The pain was usually a dull ache, at times a sharp, cutting pain in the occiput, with no throbbing. The milder attacks began at 2 a. m., passing off toward morning; the worst ones lasted all day. The headache

awakened him out of sleep almost every night. He has had no relief from any drug except an acetanilid mixture, which he had taken in large quantity. For one year he had been getting up frequently at night to urinate and had been losing weight rapidly. Because of persistently negative urine examinations, the kidneys were exonerated from blame. On physical examination the patient showed a moderate hypertrophy of the heart, with accentuated aortic second sound, and the arteries full and tense, but without marked thickening; the blood-pressure was 230 systolic, 160 diastolic, and the pulse 100 regular. The reflexes were normal. The ophthalmoscopic examination showed slight haziness of the disk outline, fulness of the veins, and one pigmented area in the right retina, otherwise nothing. The urine was 2,200 c.c., specific gravity 1.018, without albumin but with a rare hyaline cast. On July 5, 1908, following a sea-bath the patient developed intense headache, shortly afterward became delirious and then unconscious, and died in coma at noon the next day.

CASE 77.—Male, physician, aged 39. No family tendency. Had diphtheria at 13 and severe cellulitis of arm at 28, but no other infections. Consulted Dr. T. C. Janeway on Nov. 7, 1911. Four years before, a small amount of albumin and a few casts had been found on life-insurance examination, but the patient's general health was perfect. Eighteen months before, he developed what seemed ordinary sick headache once a month. The headache would begin at about 4 a. m., becoming severe; it was generally associated with vomiting and would last until the next night's sleep brought relief. The albuminuria increased somewhat, casts became more abundant, and a few red cells were present. The headaches gradually increased in frequency and were usually relieved by vomiting. During the summer of 1911 the patient exercised hard. The headaches were no worse. For a year or two he has had to urinate once at night. For two weeks before examination there had been great polyuria (five or six times at night). He had absolutely no cardiac symptoms. He had a good appetite, but lost 10 pounds in weight. On physical examination he showed a slightly forcible apex impulse in the fifth interspace, 4 inches from the midsternal line, and practically normal sounds. The arteries were small and thickened. The blood-pressure was 165 systolic and 110 diastolic, and the pulse-rate 80 regular. There were normal reflexes, no edema, and normal fundus oculi. The urine (twenty hours) was 1.060 c.c., specific gravity 1.016, and contained considerable albumin, epithelium and granular casts, red blood-cells and many leukocytes. Subsequent history: On a restricted diet, occasional purgation and sweat-baths, the patient did well for a time, but had an attack of acute gout in March, 1912. By July the headaches became very severe, about five days in the week, practically always in the early morning hours. The blood-pressure rose to 210 systolic, 130 diastolic. Hypertrophy of the heart became more evident. He lost some flesh. In September, after repeated headaches, most intense in the occipital region, he developed vomiting, gradually became irrational, and the blood-pressure reached 255 mm. at the highest. He sank into a state of chronic uremia, with high blood urea, and died after forty-eight hours of coma, with rising temperature and falling blood-pressure.

Dizziness or severe attacks of vertigo have occurred with or without headache, also drowsiness and insomnia. Apoplectic attacks, varying in severity from transient aphasia to complete hemiplegia, have characterized a group of moderate size, with a definite tendency to recur in the same person, as I shall bring out later. In eight patients an apoplectic attack was the first symptom discoverable. Onset with a convulsive seizure was a great rarity. In one case, however, four years intervened between the initial uremic convulsion and death.

Failure of eyesight as an initial or even an early symptom was noted by thirteen of the deceased patients and thirteen of those still living. My

general impression of hospital and dispensary patients, without definite figures to go by, is that in them ocular disturbance is a distinctly less frequent initial symptom. This could easily be accounted for by their failure to notice the less conspicuous disturbances which an intelligent patient will remember.

4. General Symptoms.—Of great importance are symptoms of a general or indefinite nature, for these frequently lead to the erroneous diagnosis of neurasthenia. Unusual fatigue or exhaustion after physical exertion is the commonest. Less frequent is a sense of mental tire or of depression. Pains of various kinds, neuralgic or muscular, were the first symptoms in a number of patients. Anemia is not a common early symptom, and when progressive, has an ominous significance. I have seen it associated with anorexia, persistent diarrhea and achylia. With the onset of these symptoms, a blood-pressure usually above 220 fell to about 170 mm.

Hemorrhages of one kind or another occurred as an early symptom in nineteen of the deceased and six of the living patients. Of these patients, eight and three, respectively, had noseblood. The other forms of hemorrhage were hemoptysis in nine patients, all deceased, and probably dependent on marked passive congestion of the lungs and gastro-intestinal hemorrhage, hematuria and uterine hemorrhage, each in a single case. Retinal hemorrhages have not been included in this enumeration, but have been grouped with the ocular manifestations. One patient came to me because he thought a subconjunctival ecchymosis indicated that he had high blood-pressure; he had had no previous warnings. Purpuric manifestations in the skin have not occurred early in any patient of this group.

Gastro-intestinal disturbances were not prominent in the early histories of these patients, and do not appear to me to bear any definite relation to the disease, apart from terminal chronic uremia. Among unusual early symptoms may be mentioned intermittent claudication or sudden giving out of the legs, or senile gangrene, all depending on arterial narrowing; also tinnitus aurium. Thirst of an intense nature I have discovered occasionally in association with polyuria, and it has been the indication of a bad outlook. Cough, in many cases depending on a pre-existing chronic bronchitis, but in some the evidence of chronic passive congestion of the lungs, has in a few cases preceded notable dyspnea.

5. Symptoms Depending on Other Diseases.—Diabetes has been the most common antecedent disease in this group of patients; thirty-three patients (7.2 per cent. of the whole number of 458) have been known to suffer from this for a variable length of time before the onset of any symptoms indicative of cardiovascular or renal disease. In the tabulation of polyuria as an early symptom, all cases of diabetes have been

excluded as far as possible. Prostatic or bladder disease was coincident in a number of patients. Retention of urine was the initial symptom in three of the patients, all living, and occurred very early in one of the deceased. Renal colic or the passage of a renal stone occurred in seven of the deceased and four of the living patients at an early period. Chronic bronchitis was an associated or antecedent disease in a considerable group. When severe, it necessarily introduces an error into the tabulation of dyspnea as a symptom of cardiac insufficiency associated with hypertensive arterial disease.

VII. CAUSES OF DEATH AND THE RELATION OF EARLY SYMPTOMS TO THEM

In my previous paper[1] I tabulated the causes of death and the prominent early symptoms for 100 of the cases here reported. At that time it was impossible to obtain full information for the remainder. Such information with reference to symptoms has now been secured for 212 cases, and with reference to exact causes of death for 184 patients dying prior to June, 1912. These data are shown in Table 5.

In addition, the number of times that each symptom has appeared as the first or an early symptom among the 246 patients still living on that date is shown for each vertical column. In reading the table, certain facts should be borne in mind. The tabulation is primarily one of symptoms, and several symptoms have usually occurred together in the same patient. The footings of the vertical columns, therefore, represent the number of cases in which the particular symptom has occurred before the date of my first examination, or definitely at an early period of the illness. Dyspnea on exertion and paroxysmal dyspnea occurred in association so frequently that they have been grouped in a single column, not separated as in my previous study. Only the more prominent symptoms, those occurring with considerable frequency, are here included.

The discussion of the credibility of the diagnoses under the various categories in the early part of this paper should be borne in mind. It should be especially remembered that the deaths credited to uremia presumably contain some cases of apoplexy, and that pericarditis undoubtedly occurred much more frequently. Whenever a terminal uremia carried off a patient after a long period of cardiac failure, the death has been credited to cardiac insufficiency, but apoplexy ending the scene has always been considered the immediate cause of death. Also, the endeavor has been made as much as possible to eliminate from the patients dying of edema of the lungs all those with the common, gradual terminal edema, and to include only those with acute suffocative edema of the lungs. It is not probable, however, that this has been entirely successful. The thirteen patients dying of complicating acute infectious disease comprise

TABLE 5.—The Relation of Prominent Early Symptoms with High Blood-Pressure to Causes of Death

Symptoms												Deaths					
													Male Pct. of Total Known, 137		Female Pct. of Total Known, 47		
Dyspnœa	Edema of Lungs	Anginoid Pain	Edema of Legs	Polyuria	Visual Disturbance	Headache, Typical	Hemiplegic Attacks	Vertigo	Loss of Flesh	Fatigue, Pains	Albu., Casts Acc. Discov.	Causes of Death	No.	Pct.	No.	Pct.	Total
48	4	11	15	11	2	3	4	2	10	7	4	Gradual cardiac insufficiency	48	35.0	12	25.5	60*
18	1	3	1	29	9	16	7	3	13	10	4	Uremic convulsions, coma or gradual uremia.	31	22.6	15	31.9	46†
11	0	2	3	1	2	4	5	3	3	7	1	Cerebral apoplexy or its results...	20	14.6	9	19.1	29†
3	0	6	2	1	0	1	1	0	0	0	1	Angina pectoris ..	10	7.3	0	....	10
6	3	1	1	2	0	0	0	0	1	2	0	Edema of lungs...	6	4.4	1	2.1	7
2	0	0	0	0	0	1	1	0	0	1	0	Progressive anemia	1	0.7	2	4.3	3
0	0	0	1	0	0	0	0	0	0	0	0	Pericarditis	1	0.7	0	....	1
3	0	3	2	1	0	0	0	0	0	3	1	Complicating acute infectious disease	9	6.6	4	8.5	13
1	0	1	0	1	0	2	1	1	1	3	0	Other, accidental causes	7	5.1	2	4.3	9
11	3	7	1	5	0	3	5	0	3	3	1	Unknown	25	....	3	....	28
3	0	1	0	1	0	1	0	0	1	1	0	Sudden	4	2.9	2	4.3	6
106	11	35	26	52	13	31	24	9	32	37	12‡		162		50		212
PERCENTAGE OF TOTAL NUMBER DECEASED, 212																	
50.0	5.2	16.5	12.3	25.0	6.1	15.0	11.3	4.2	15.0	18.0	6.0						
SYMPTOMS IN LIVING PATIENTS																	
94	3	42	27	45	13	29	10	35	9	59	13§						
PERCENTAGE OF TOTAL NUMBER LIVING, 246																	
38.2	1.2	17.0	10.9	18.2	5.3	12.0	4.0	14.2	4.0	24.0	5.3						

* These sixty cases were 32.6 per cent. of 184 known deaths. † These seventy-five cases were 40.8 per cent. of 184 known deaths.
‡ All men. § Five women.

nine cases of pneumonia. "Other accidental causes" consist of automobile accidents, deaths from surgical operation, drowning, carcinoma and other wholly unrelated diseases. The six sudden deaths are presumably from angina pectoris or apoplexy.

The results of this tabulation are very similar to those obtained in the study of 100 cases already reported[1] (see Table 2 of that paper). They do not materially alter the conclusions then drawn. They permit, however, of more definite deductions. They may be studied from three points of view: (1) the relative proportion of deaths from the various causes enumerated; (2) the numerical relations of the various symptoms and symptom groups to one another and to the causes of death; and (3) the comparative frequency of the individual symptoms in the patients already deceased and in the group of those still living.

1. Distribution by Causes of Death.—The type of death was known for 184 of the 212 deceased patients; for 28 it could not be stated exactly. While the largest total number, 60 (32.6 per cent.), died a gradual cardiac death—if one groups together deaths from uremia and from apoplexy into a "cerebral" group, as did Bright, 75 (40.8 per cent.) are thus included. It is particularly interesting to note the almost exact correspondence of this with Bright's tabulation of the causes of death which he traced in 70 of his cases, 30 of the patients (42.8) dying a cerebral death with apoplexy, coma or convulsions. Cardiac insufficiency was a conception which did not exist in Bright's day, and it is impossible from his figures to obtain any clear idea of how many of his cases should be classed in this category. If in Table 5 one considers the deaths from angina pectoris, from edema of the lungs, from pericarditis, and probably some of the sudden deaths as cardiac, then it is evident that the two main groups—the cardiac and the cerebral—are almost equal, over 40 per cent. dying in each of these ways, about 12 per cent. of complicating disease, accident or unrelated causes; while a very small number (1.6 per cent.) ran the course of a progressive wasting disease with severe anemia.

A. Sex Distribution: At the right of Table 5 are two columns indicating the total number of men and women dying in each of the groups, and the percentage relations which these numbers bear to the total number of deceased males and females. While variation from the general sex distribution of the whole group in the three larger categories is shown only in the deaths from uremia, this difference is not so great as to be free from the possibility of chance. The next two categories, however, death by angina pectoris and by acute edema of the lungs, show a divergence from the sex distribution of the group so extreme as, I think, to indicate clearly a definite difference in sex predisposition. Not a single woman died in an anginal seizure and only one in an attack of edema of the lungs, as against, respectively, ten and six men.

B. Age in Relation to Causes of Death: A tabulation of the ages by decades of those dying in each group, giving the median or middle point, the mode or the largest number for any decade, as well as the second greatest number is shown in Table 6.

TABLE 6.—AGES IN RELATION TO CAUSES OF DEATH

Causes of Death	Males		Females	
	Mode*	Median	Mode	Median
Cardiac insufficiency..	50-59 60-69	50-59	60-69 50-59	50-59 ....
Uremia (gradual and coma)	40-49 50-59	50-59	60-69 40-49..	50-59 ....
Cerebral apoplexy ...	50-59 60-69	50-59	60-69 ?	60-69 ....
Angina pectoris	60-69 50-59	60-69	No women	....
Acute infectious disease (mostly pneumonia)	50-59 70 and over	50-59	70 and over No other	70 and over ....

* The two sets of figures for the mode indicate the largest number and the second largest number for each group.

The number of patients dying of edema of the lungs, seven in all, is too small to use as a criterion of tendencies.

A comparison of Table 6 with Chart 1 shows that the mode, 50 to 59 in the cardiac and the apoplexy groups for the males, is the same as the mode for the total deceased males. On the other hand, for the females the mode in the cardiac, the uremic and the apoplexy groups is a decade higher, that is, 60 to 69, which agrees with the mode for the total number of deceased females as shown in Chart 1. It will be noted that the mode for the uremic group for the men (40 to 49) is a decade lower than the median for the total group of deceased; but the mode for angina pectoris (all men) is 60 to 69 years, which is higher than the average mode (50 to 59) for the men. As will be seen, the median, or the dividing point, for the men is the 50 to 59-year group for all the deaths except angina pectoris, in which it is a decade higher; while for the women, a median of 50 to 59 years applies only to the cardiac and uremic, being a decade higher for the apoplectic, and still a decade higher (70 years and over) for those dying of acute infectious diseases.

A study of the second largest groups is of interest as showing tendencies. For the men dying a cardiac death there seems to be a tendency toward a decade higher than the median for that group, and for the women there is a tendency to approach the median. In the second largest

group for the uremic men there is a tendency of coincidence with the median, while for the women there is an apparent tendency for death at an earlier age, 40 to 49 years. The tendencies for the men dying of apoplexy, as expressed in modes and median, are exactly like those of the men dying a cardiac death.

It seems probable that this table furnishes an indication of the composite nature of the uremic group, made up in part of elderly arteriosclerotics, in part of patients with contracted kidneys, and younger persons with inflammatory kidney lesions.

C. The Relation of Blood-Pressure to Causes of Death.—Table 7 shows from various points of view the relation between the height of the observed blood-pressure and the final cause of death.

TABLE 7.—HEIGHT OF BLOOD-PRESSURE IN RELATION TO CAUSE OF DEATH

	Special Group		Percentage at or Below Median (220) for Whole Group	Percentage Above Median (220) for Whole Group
	Mode	Median		
Cardiac insufficiency..	215-220	210	68.3	31.7
Uremia (gradual and coma)	215-220	220	52.1	47.9
Cerebral apoplexy.....	225-230	225	41.4	58.6
Angina pectoris.....	175-180	200	80.0	20.0
Edema of lungs.....	245-250	240	28.6	71.4
Acute infectious disease (mostly pneumonia	175-180	185	84.6	15.4

NOTE.—Of the "sudden" deaths not included in the foregoing there were five in all — four men and one woman. The blood-pressures of the men were: One 175, two 210, one, 240 mm.; and the one woman had a pressure of 260.

The figures speak for themselves and require little comment. The differences are so striking as practically to preclude the operation of chance, except in the case of the small group of patients (seven in all) dying of acute edema of the lungs. Both the mode and the median for this group and the number of cases over 220 mm. are the highest noted for any of the groups. It is significant that the two cerebral groups, those dying of uremia and of apoplexy, show a tendency to marked hypertension, the apoplexy cases especially, while the patients dying of gradual cardiac insufficiency have a median of blood-pressure below the median for the entire group, and those dying of angina pectoris a still lower one, the lowest of all being found in the case of patients dying of acute infections. This table would seem to indicate that, other things being equal, a systolic blood-pressure persistently above 200 mm. constitutes a certain presumption in favor of termination by uremia or apoplexy.

The discussion of factors bearing on duration of illness, from the first discoverable symptoms to death, involves a number of considerations which must be taken up in relation to the symptoms and will, therefore, be discussed subsequently.

2. Distribution by Symptoms.—Table 5 shows the number of times that each of the more important symptoms has been mentioned in the anamnesis of these patients. Since the vast majority complained of more than a single symptom, it must be clearly understood that the footings of the vertical columns represent only the total number of deceased patients who had at some time during the early part of their indisposition noted the particular symptom tabulated in that column. The totals of the vertical columns must not be added together and compared with the total number of patients. The four columns to the left of the double ruling contain the symptoms referable to the cardiac changes associated with high-blood pressure. The columns to the right contain symptoms referable to the kidney and the eyes, circulatory and toxic cerebral manifestations, symptoms due to disturbed nutrition, and the indefinite fatigue or pains which are often complained of.

The most striking fact about the table is the frequency of dyspnea as compared with any other symptom. It occurred in exactly half of all the patients. The next most frequent symptom was urinary disturbance, complained of by somewhat less than a quarter of all the patients. It must be remembered that this includes cases of urinary disturbance from local causes which could not be separated from those of the patient with true nephritic polyuria. The number of patients with anginoid pain on exertion (35 in all) will, I think, seem surprisingly large to those whose experience is mainly in hospital wards; and on the other hand, the 13 patients with early disturbance of vision will seem few. Both symptoms, I believe, indicate that persistent high blood-pressure in such a group of well-to-do persons is the evidence of what is predominantly a circulatory rather than a renal disease. This is again indicated by the early occurrence of hemiplegic attacks in 24 of the patients, and of edema of the legs in 26. That 37 of the patients should have sought medical advice largely because of unusual fatigue or of neuralgic or muscular pains suggests the need of great caution in making the diagnosis of neurasthenia in persons past middle life. It should never be made without an instrumental determination of the blood-pressure. In only 12 of the 212 deceased patients was the existence of disease revealed by the discovery of albumin and casts in the urine, and in only four by the discovery of high blood-pressure in men who considered themselves in perfect health and who, on cross-examination, could not remember any departure from normal health.

Had the anamesis not been carefully taken with reference to the existence of symptoms easily overlooked by the patient himself, the num-

ber of these accidental discoveries would probably have been greatly increased. They demonstrate the value of systematic examinations in revealing unsuspected disease and suggest the wisdom of an occasional examination of the urine and the blood-pressure in all persons past middle life. A yearly examination by the family physician of all his patients should become the rule. It is certainly as much called for among the elderly as among schoolchildren, and is in line with the progress of preventive medicine. But a careful physical examination is not the sole means of detecting disease. It is equally important that the physician should understand the art of history-taking and the significance of symptoms.

A. The Relation of Blood-Pressure to Early Symptoms.—The relations of the blood-pressure reading to some of the symptom groups is shown in Table 8.

TABLE 8.—HEIGHT OF BLOOD-PRESSURE IN RELATION TO PROMINENT EARLY SYMPTOMS

Symptoms	Deceased Blood-Pressures				Living Blood-Pressures			
	165-220 Per Cent.	Over 220 Per Cent.	For Special Groups		165-220 Per Cent.	Over 220 Per Cent.	For Special Groups	
			Modes	Median			Modes	Median
Dyspnea	56.6	43.4	235-240 185-190	220	57.4	42.6	175-180 215-220	200
Anginoid pain	68.6	31.4	175-180	195	78.6	21.4	175-180 185-190	190
Polyuria	44.2	55.8	215-220 225-230	230	75.6	24.4	185-190	200
Headache, typical	51.6	48.4	215-220 225-230	220	72.4	27.6	215-220 195-200	210+
Hemiplegic and apoplectic attacks	47.6	52.4	225-230	220+	88.9	11.1	185-190	190
Vertigo	44.4	55.6	215-220	220+	71.4	28.6	175-180	200
Loss of flesh	53.1	46.9	215-220	220	88.9	11.1	175-180	180+
Neurasthenic symptoms (fatigue and pains)	62.2	37.8	185-190 175-180	215	83.1	16.9	175-180 165-170	190+
Albumin and casts (accidental discovery)	58.3	41.7	215-220	220	76.9	23.1	185-190	190+

NOTE.—Computations have been made on the basis of 220 mm., which is the median for the group of deceased patients.

The main indications which this table afford are that the patients with anginoid pain and with the indefinite neurasthenic symptoms tend to run below the median blood-pressure, while the patients with headache, polyuria and apoplectic and hemiplegic attacks tend in the opposite direction.

B. The Relation of Early Symptoms to Causes of Death.—A comparison of the frequency of individual symptoms in the different groups arranged by causes of death (Table 5) brings out certain prominent clinical types which hypertensive cardiovascular disease assumes. Cardiac symptoms occur three times as frequently in patients who eventually die a cardiac death as in patients who die a uremic death, and five times as often as in those who die of apoplexy. What I have previously designated as "typical" headache, on the other hand, has occurred in sixteen patients who subsequently succumbed to uremia as against three who died a cardiac death, and four who died of apoplexy. Urinary disturbance was more than twice as frequent in the group terminating by uremia, and visual disturbances more than four times, notwithstanding the fact that the total number of patients was only three-fourths of the total dying of heart-failure. The relation of hemiplegic attacks to the eventual death is less striking, but taken in relation to the totals, it indicates about a double frequency of this symptom in those dying a cerebral death of one or the other form. The relation of anginoid attacks to the probability of death in an anginal seizure is a matter of some interest. Four of the ten patients dying of angina pectoris did not have anginal attacks early in the disease, and of thirty-five patients who complained of definite precordial or substernal pain or oppression on exertion, only ten finally died in an anginal paroxysm. Eleven persons with anginoid pain died a gradual cardiac death. In the deaths from angina pectoris and acute suffocative edema of the lungs, however, previous attacks of a similar nature figure in the anamnesis of a high proportion of the patients.

3. The Relation of Early Symptoms in the Deceased and Living Groups.—The relative frequency of certain of the early symptoms among the deceased as compared with the living (Table 5) shows interesting resemblances and still more interesting differences. Dyspnea was a little less frequent among the living; early anginal pain and early edema of the legs were almost identical. Attacks of edema of the lungs, however, were conspicuously less numerous in the living, which rather confirms my belief in their serious prognostic significance. Urinary disturbances and typical headache show about the same relations as the dyspneas in the two groups. The accidental discovery of albumin and casts likewise occurs in the same ratio, but among the living were five women; there were no women with this finding in the deceased group. This indicates perhaps an increasing knowledge of this type of disease among the laity and consequent increase in precautionary visits to a physician. Hemiplegic attacks were much less frequent among the living. The whole question of the significance of apoplectic attacks, however, will be considered by itself later. Vertigo or dizziness, judged by its incidence in the two groups, must be considered a symptom of trivial moment. It

seems to be decidedly more common in the elderly arteriosclerotic patients than in those whom one would classify as cases of primary contracted kidney. Visual disturbances show a rather unimportant difference, which it is difficult to explain.

No symptom was more strikingly different in the group of the deceased and the living patients than loss of flesh. From this, I am inclined to the conclusion that this symptom must be looked on as of serious omen. In order to be quite safe in such a conclusion, however, I restudied the records with reference to the duration of illness in the deceased patients showing this symptom and the time before death when emaciation began. Of the thirty-two deceased patients who showed this symptom early, nineteen died in five years, thirteen in less than four years, and eleven lived six years and over from their initial symptom. In these patients, loss of flesh was manifested in three ways. One patient lost a moderate amount of weight at the start of her illness, some of which was regained subsequently. She died five and one-half years later. Six patients exhibited a slow and steady decline in weight of only moderate extent, over periods varying between five and eleven years. These two types of loss in weight are evidently without serious import. Seven patients, however, showed progressive and marked loss of flesh, three dying in less than one and one-half years, one in two and one-half years and the remaining three in from three to three and one-third years after emaciation set in. It seems to me conclusive from this that rapid, continued loss of flesh must be considered as pointing toward a fatal termination in less than the average time for patients with high blood-pressure.

Fatigue and pains, on the other hand, showed a relation to an earlier stage or a milder type of disease, by occurring almost twice as frequently in the patients still living.

VIII. ADDITIONAL DATA FROM HISTORIES AND PHYSICAL EXAMINATIONS

1. Apoplectic Attacks.—An attempt was made to discover the total number of deceased patients in whom apoplectic or hemiplegic attacks, or their analogues, occurred at any time in the course of the disease. They were mentioned by fifty-eight patients in all, forty-three men and fifteen women. These are, respectively, 21.1 per cent. of the total males and 31.2 per cent. of the total females, whose type of death is known. The sex incidence of apoplexy as a cause of death or of hemiplegic attacks during life is not materially different in the two sexes.

2. Anginal Attacks.—I have been especially interested in the frequency of anginoid pain among these patients. Of the deceased, 32, or 19.6 per cent. of all males, and 6 women, or 12.2 per cent. of all females, had this symptom in some degree. Among the living, however, it is

surprising to find that 20, or 19.6 per cent. of all the women, complained of anginoid pain as against 26 men, or 18 per cent. of all the males. When one compares this with the deaths from angina pectoris, all ten of which were in men, the only reasonable explanation would seem to be that the milder anginoid attacks are commoner in women than in men, and that when they occur, women avoid sudden and forced exertion and excitement far better than men; for this reason, for the most part, they escape death in an anginal paroxysm. For the rest, it is probable that syphilitic aortitis is commoner among men than among women, and is the cause of some of the anginal deaths.

3. Cardiac Arhythmias.—My record of the existence of arhythmia among these patients depends either on my detection of it at the time of examination, on the definite knowledge of it obtained from the patient's physician, or a definitely satisfactory description of the arhythmia by the patient himself. My data are, therefore, defective, and greatly underestimate the total frequency of arhythmia which would have been found had these patients been followed throughout a period of years. Of the 212 deceased patients, 71 had some degree of cardiac insufficiency at the time of examination. Only 8 patients had the perpetually irregular pulse indicative of auricular fibrillation. It is noteworthy to record that 6 of these 8 patients were treated with digitalis and the results were known: the result was satisfactory in four, slight in one and without benefit in the other. Contrasted with this were 6 patients with failing hearts and regular rhythm, of whom 4 responded well to digitalis, two brilliantly. The relief of dyspnea was especially notable as Miller[8] reported last year. Of the other arhythmias, extrasystoles were noted in 9 patients, paroxysmal tachycardia in 3, heart-block in one, and an unspecified arhythmia in one. Eight of the patients complained of serious palpitation. Among the 246 living patients, only 25 had insufficient hearts when examined. Only 2 patients had the evidence of auricular fibrillation; 17 patients had extrasystoles, 4 paroxysmal tachycardia, one heart-block, one a marked sinus arhythmia and one an unspecified irregularity.

I have been somewhat impressed with the less frequent occurrence of fibrillation of the auricles in the insufficient heart secondary to high blood-pressure as contrasted with valvular disease. My evidence for this is not altogether satisfactory, as it rests in part on the incomplete figures just given. A study of the records of 75 patients with auricular fibrillation, electrocardiographically recorded by Dr. Stuart Hart at the Presbyterian Hospital, showed that 14 had a blood-pressure above 180 mm.; this is only one-fifth. This figure could have absolute value only if it were known what proportion of the cases of cardiac insufficiency at the hospital were due to hypertensive disease and what proportion to valvular disease during the same period. This I have been unable to calculate.

8. Miller, Joseph L.: Tr. Assn. Am. Phys., 1912, xxvii, 137.

4. Evidence of Cardiac Hypertrophy.—My records contain statements as to the existence of evidence of cardiac hypertrophy and its degree in 193 of the deceased patients and 244 of the living. What I have considered such evidence has been enlargement of the percussion area, displacement of the apex beat downward and to the left, or a definite lifting character of the impulse, singly or combined. No roentgenographic studies have been made. The accentuated aortic second sound has not been considered such evidence, but has been tabulated separately. Table 9 has been prepared from my records.

TABLE 9.—EVIDENCE OF CARDIAC HYPERTROPHY IN 437 PATIENTS

	Deceased*	Living
None	8	89
Questionable	4	5
Slight	41	98
Moderate	96	83
Marked	44	19
Total	193	244

* For nineteen of the deceased patients the data as to existence of non-existence of hypertrophy were not recorded.

This table, of course, does not indicate the existence or non-existence of cardiac hypertrophy, but only my ability to detect it. It is interesting especially as an indication of the very considerable number of patients in whom even a careful physical examination will fail to show a hypertrophied heart, and that only the sphygmomanometer makes the diagnosis of this type of cardiovascular disease definite. The tabulation is particularly valuable, therefore, as indicating the importance of instrumental blood-pressure observations in diagnosis. Of further interest is the difference between the two groups of patients. Not only was proof of cardiac hypertrophy lacking in nearly five times as many of the living as the dead, but the slighter grades of hypertrophy were numerically more frequent and the marked grades much less. It is altogether probable, therefore, that the group of the living is made up of persons at an earlier stage of the cardiovascular disease.

5. Accentuation of the Aortic Second Sound.—A definite note as to the character of the aortic second sound was made on 163 of the deceased and 226 of the living patients. My findings are shown in Table 10.

It will be seen that no accentuation of the aortic second sound could be heard in a considerable proportion of the cases — in thirty-eight (23.3 per cent. of the 163 deceased for whom this information was recorded), and sixty-seven (29.6 per cent.) of the living. This information is within

the limits of the personal equation of the examiner — absolute, not merely relative, as are the data regarding cardiac hypertrophy. The causes for absence of accentuation of the aortic second sound in hypertension are various; emphysema of the lungs, marked obesity, senile rigidity of the thorax and other unknown conditions modify the transmission of vibrations. Beyond these, it seems to me clear that there are conditions within the heart and aorta in these patients which modify the intensity and pitch of the aortic second sound in addition to the aortic blood-pressure. For instance, over the dilated aorta of syphilitic aortitis an extremely loud, ringing sound may be heard when the blood-pressure is normal. In this connection I wish to emphasize again the fact that without instrumental blood-pressure determinations, many cases of hypertension must inevitably be overlooked, even by the most expert examiner, as in many of these patients not a hypertrophied heart, an accentuated second sound, or a pulse which impresses the examiner as tense will be

TABLE 10.—INCIDENCE OF ACCENTUATION OF AORTIC SECOND SOUND IN 389 PATIENTS

	Deceased	Living
None	38	67
Questionable	1	1
Slight	21	55
Moderate	75	88
Marked	28	15
Total	163	226

found. So far as the further evidence of the table goes, very marked accentuation of the aortic second sound was proportionately more than twice as frequent in the deceased as in the living groups, and moderate accentuation was about equal, the slighter degrees greatly preponderating in the living. This shows a rough correspondence with the median for the blood-pressures of the two groups, as would be expected.

6. Evidence of Arteriosclerosis of the Peripheral Arteries.—The histories studied include definite statements as to the condition of the larger peripheral arteries in 171 of the deceased and 231 of the living patients. My findings are shown in Table 11.

Of particular note in this table is the large number of patients in each group in whom the radial, brachial and temporal arteries were free from evident thickening, elongation or calcification. It demonstrates how independent permanent high blood-pressure is of arteriosclerosis in the ordinary sense, that is, arteriosclerosis of the larger accessible peripheral vessels. It is the reverse side of the well-known fact that extensive

arteriosclerosis of these vessels is frequently found associated with blood-pressure not above the normal. The slight degrees of arterial thickening are especially evident among the patients still living and the marked among those that have died. The evidence here, as for cardiac hypertrophy, is therefore in the main that arteriosclerosis of the larger peripheral vessels should be looked on as a secondary lesion similar to

TABLE 11.—EVIDENCE OF ARTERIOSCLEROSIS IN 402 PATIENTS

	Deceased	Living
None	65	117
Questionable	1	0
Slight	14	46
Moderate	60	55
Marked	31	13
Total	171	231

the cardiac hypertrophy. This is further brought out by an examination of the eventual causes of death in those patients who showed moderate or marked degrees of arteriosclerosis. By "slight" arteriosclerosis in the preceding tabulation I have meant arteries which were just distinctly palpable when empty, or showed slight tortuosity. This is so regular a finding in persons past middle life that it does not seem to me to have

TABLE 12.—THE RELATION OF MODERATE OR MARKED ARTERIOSCLEROSIS TO CAUSES OF DEATH IN NINETY-ONE PATIENTS

Causes of Death	Moderate	Marked	Totals
Gradual cardiac insufficiency	13	6	19
Uremia	18	13	31
Cerebral apoplexy	10	3	13
Angina pectoris	1	0	1
Edema of the lungs	2	3	5
Acute infectious disease	1	1	2
Other causes, unrelated, etc.	10	2	12
Unknown	5	3	8
Total	60	31	91

any strict relation to the disease here studied. The considerable degrees of arteriosclerosis, however, are evidence of more than mere wear and tear. A tabulation of all the cases showing more than the slighter grades is shown in Table 12.

To my great surprise, Table 12 shows a marked preponderance of disease of the large peripheral arteries among the patients dying of uremia. I had expected that the group dying of insufficient hearts would

contain the bulk of the arteriosclerotics. My general impression was that arteriosclerosis was associated with sclerotic changes in the coronaries and consecutive myocardial, nutritional disturbances, leading to myocardial insufficiency. The examination of these histories has shown, however, that these striking degrees of arterial thickening and elongation frequently occur in young persons with the picture of so-called primary contracted kidney or other primary renal disease. Some of these patients have been under 40 years of age. But again, a large number of the patients with anginoid pain and presumptive coronary sclerosis have been free from any traces of peripheral arterial thickening. This emphasizes what is beginning to be more generally appreciated: that the distribution of arteriosclerotic lesions is most variable; that extensive cerebral or coronary arterial disease may exist without any evidence of thickening of the accessible arteries of the extremities; that certain causes for arterial disease, the *Spirochaeta pallida*, for instance, have a strict elective affinity for limited portions of the arterial system — all facts tending to suggest that the arterial system cannot be looked on as a whole in the development of its pathological processes, but that local differences in susceptibility to disease exist, and that local causes play a considerable part in the distribution of its lesions.

Further, this table strengthens the argument drawn from the preceding table (Table 11) that peripheral arteriosclerosis in hypertensive disease must be looked on usually as result, not cause. This view seems to be taken by Jores,[9] and has been a common one among clinicians. It also fits in well with Marchand's studies in arteriosclerosis,[10] which go to show that cardiac hypertrophy is not as a rule associated. For this reason it seems to me that to speak of the type of disease under discussion as arteriosclerosis or hardening of the arteries, as is so frequently done, is altogether erroneous and productive of false views of the causation of high blood-pressure.

7. *Urinary Findings. A. Albumin and Casts in the Urine.*—Careful urinary examinations were made in the majority of cases at the time of my physical examination. Only the analyses made in my own laboratory or in that of my father have been considered in studying the significance of these urinary findings. The significance of this information is wholly diagnostic. I have no data from which any statement can be made as to incidence of albuminuria and cylindruria during the course of hypertensive cardiovascular disease. It was of interest from the point of view of the usefulness of a single urine analysis, as a means of diagnosis of this type of disease, to tabulate my findings.

9. Jores: Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie vom pathologisch-anatomischen Standpunkt, Verhandl. deutsch. path. Gesellsch., 1908, xii, 187.

10. Marchand: Verhandl. d. Cong. f. inn. Med., 1904, xxi, 60.

Of the 212 deceased patients, 21 showed neither albumin nor casts in the urine when examined; and of the 246 patients still living, 95 had urines negative in both these respects. In 23 of the deceased and 19 of the living, albumin was found without casts; in only two and one case, respectively, in any considerable amount. In 17 of the deceased and 32 of the living, casts were discovered in urine which did not show albumin by the nitric acid ring test; again, in only one and two patients, respectively, were they numerous.

Of the deceased patients, 114 out of the 182 of whom I have definite information in this respect, or 62.6 per cent., had definite amounts of albumin and casts; of the living, 85 out of 236 of whom I have records, or 36 per cent., showed both albumin and casts. In 25 of the former and 42 of the latter there were but few casts and a trace of albumin. In the remainder, 89 (48.9 per cent.) of the deceased and 42 (17.8 per cent.) of the living, albuminuria was moderate or marked; and casts, except in a few cases, were numerous. No study as to types of casts has been made. Information on this point, which is beginning to come from the life-insurance companies in such studies as those of Barringer,[11] will have much more positive prognostic value.

A tabulation of those cases showing more than a trace of albumin with casts, in which the causes of death were known, is given in Table 13.

TABLE 13.—Relation of Moderate or Marked Albuminuria with Casts to Causes of Death in Seventy-Nine Patients

Causes of Death	Number
Gradual cardiac insufficiency	24
Uremia	30
Cerebral apoplexy	8
Angina pectoris	3
Edema of the lungs	3
Progressive anemia	2
Pericarditis	1
Other, accidental, causes	5
Sudden	3
Total	79

It is clear that a negative urine examination has the very slightest value in excluding the existence of cardiorenal disease of the type presented by these patients. This, of course, is well known, but cannot too often be insisted on. These urinary studies also bring out the mixed character of the material investigated. Large amounts of albumin and large numbers of casts belong especially with the true chronic inflammatory lesions of the kidney. They are also to be expected during periods of marked cardiac insufficiency. For this reason, the deceased group showed their presence much more frequently than the living group.

11. Barringer, Theodore B.: The Prognosis of Albuminuria with or without Casts, The Archives Int. Med., 1912, ix, 657.

B. Specific Gravity of the Urine.—Twenty-four-hour urine specimens were not obtained from the majority of the persons studied. The urine specimens examined, however, were always mixed specimens from afternoon, night and morning, representing about sixteen hours out of the twenty-four. The records of specific gravity obtained in such specimens have only a relative value, and they are introduced here without a desire to draw more than very guarded conclusions.

TABLE 14.—SPECIFIC GRAVITY OF URINES, DECEASED AND LIVING

	Deceased	Living
Normal, 1.015 to 1.022.....	68	135
Low, below 1.015	78	43
High, above 1.022	25	50

TABLE 15.—SPECIFIC GRAVITY OF URINES IN RELATION TO CAUSES OF DEATH *

Causes of Death	Urines				Total Cases
	Normal	Low	High	Unknown	
Cardiac insufficiency.	23	24	4	9	60
Uremia	13	24	5	4	46
Apoplexy	10	9	5	5	29
Angina pectoris.....	5	3	2	0	10
Edema of the lungs..	3	1	2	1	7
Acute infectious disease	5	1	4	3	13

* The patients dying of progressive anemia, pericarditis, unknown, and sudden deaths are not included.

Two things stand out prominently in Tables 14 and 15: first the double frequency of low specific gravity in the whole deceased group as against the whole living group; secondly, the finding of low specific gravity more frequently than normal or high specific gravity definitely only in those patients dying of uremia. In those dying a cardiac death, about an equal number showed a low as a normal specific gravity; in those dying of apoplexy and from intercurrent infections, the greater number had urines of normal or increased specific gravity. The relation, therefore, is manifest between a low specific gravity and the type of disease in which symptoms of renal insufficiency were prominent. On the other hand, low specific gravity urine occurred with such numerical frequency in individual cases of the other types as to have only relative value in prognosis.

8. The Relationship of Diabetes to High Blood-Pressure.—The 458 cases studied contain thirty-six (7.9 per cent.) diabetics. This number is

probably well above what it might be with a different selection of material, for my practice has included a rather unusual number of cases of diabetes. The proportion, however, is obviously too large to be explained by mere chance. The effect of diabetes on blood-pressure has been the subject of some discussion. Potain[12] included diabetes with chronic nephritis as one of the causes of extreme hypertension. My view has always been that the effect is altogether indirect,[13] the result of the well-known frequency of arterial disease in elderly diabetics. The relation here may well be a double one—primary arterial changes in the pancreas producing the diabetes, or the diabetes leading to wide-spread arteriosclerosis. Certainly, pure diabetes in young persons, leading to death by coma, never is associated with high, but usually with low blood-pressures. My views have been substantiated by Elliott's[14] studies. In all but three of these patients, as already mentioned, the diabetes was recognized before the high blood-pressure or symptoms clearly referable to it were discovered.

IX. DATA BEARING ON DURATION OF DISEASE

In dealing with conditions of such insidious onset, in which the lesions without doubt long antedate the development of symptoms, it is manifestly impossible to arrive at an exact estimate of the possible or even usual duration. I have endeavored in each case to collate from my records the facts bearing on duration. These facts are: (1) the length of time before death during which any symptoms reasonably attributable to cardiovascular or renal disease existed, calculated to the date of death in the case of the deceased and to June 1, 1912, in the case of the living; (2) the duration of life after high blood-pressure was detected by me, or in the case of the living, the time which had elapsed between my finding of hypertension and June 1, 1912.

1. Duration of Life from First Symptom.—The first set of facts is shown in graphic form in Charts 5 and 6, which represent complete information on this point obtained about 187 deceased and 244 living patients. The character of the curves for the living and the deceased is strikingly similar. It is probable that a sufficiently large number of patients would obliterate the lesser irregularities. The median, also, is identical — four years for men and five years for women, in both the deceased and the living groups. The high point of the tabulation for the deceased is reached at one year, while for the living a second apex is

12. Potain, C.: La pression artérielle de l'homme á l'état normal et pathologique, Paris, 1902.

13. Janeway, Theodore C.: The Clinical Study of Blood-Pressure, New York, 1904, p. 236.

14. Elliott: Arthur: The Clinical Study of Blood-Pressure Variation in Diabetes and their Bearing on the Cardiac Complications, Jour. Am. Med. Assn., 1907, xlix, 27.

found at three years. Whether this is more than accidental, I cannot tell. Patients dying in less than one year from the first development of symptoms represent to a much larger extent than the others, patients seen in their terminal illness, who were not in a position to give accurate data as to early and minor symptoms. The patients still living represent to a much larger extent those seen in office practice from whom much

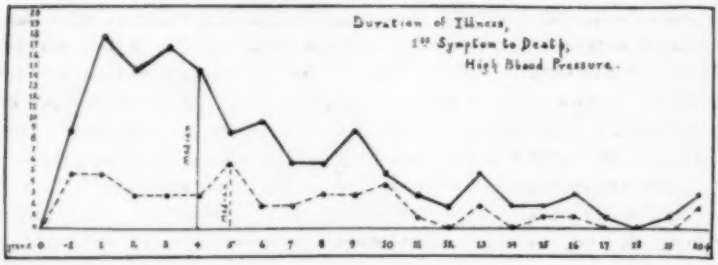

Chart 5.—Duration of illness, first symptom to death, high blood-pressure; solid line, males, 141; broken line, females, 46; total, 187.

more complete information could be obtained. It is probable that this is the real explanation of the early high point for the males in Chart 5. This much is clear, that from the time of the development of symptoms indicative of cardiovascular or renal disease, four years will witness the death of half of the men and five years of half of the women. By the

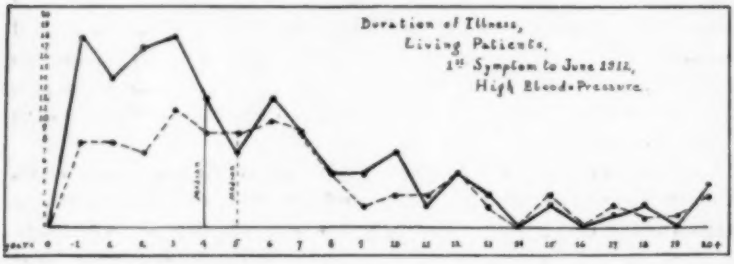

Chart 6.—Duration of illness, living patients, first symptom to June, 1912, high blood-pressure; solid line, males, 143; broken line, females, 101; total, 244.

tenth year, half of the remainder will also have died, leaving both for the men and the women a quarter of the whole group whose duration of life is ten years or over. These patients of long duration diverge from one another so widely in the length of life as to warrant entirely separate consideration; hence they have been subjected to special study. They are shown in abstract form in Table 16.

While it is impossible to discuss all the interesting features here presented, certain facts are noteworthy. Seven of the thirty-seven patients were elderly diabetics. In five of the seven, the first symptom was glycosuria or some symptom referable to the diabetes, and it was impossible to distinguish at what period of their diabetes the arterial hypertension supervened. In two, cardiac or renal symptoms occurred at the onset (Cases 103 and 182). In Case 182 the patient, a man, had general edema for fourteen years before death and anginoid pain early in his disease; he died at the age of 62, of an insufficient heart, and four years before death the blood-pressure was 170 mm. In Case 103 the patient, a woman, had edema of the legs fifteen years before her demise. She had dyspnea, both on exertion and paroxysmal, many years before death which followed at the age of 64 from apoplexy; her blood-pressure one year before death was 230 mm. systolic and 130 diastolic.

One of the most interesting patients (Case 211) was a man who at the age of 50 developed mild intermittent claudication. He subsequently suffered from neuralgic pains, vertigo and headaches, and had an attack of left-sided numbness. A blood-pressure reading taken five years before death was 185 systolic, 100 diastolic. He was drowned in the *Titanic* disaster at the age of 67, with considerable expectancy of life before him.

In three cases, 17, 86 and 172, the first symptom was accidental discovery of albumin and casts. The duration of life thereafter was 19, 22 and 13 years, respectively.

A very striking case was Case 75, in a girl who had an acute nephritis following diphtheria at the age of 9. The clinical course was characterized by a striking hemorrhagic tendency, recurring hematuria with fever, uterine and retinal hemorrhages, consecutive anemia, oliguria, with headache and vomiting. After ten years from the onset of symptoms she died of anemia consecutive to her losses of blood. The blood-pressure at the age of 19 was 210 mm. systolic and 110 diastolic. There was an associated endocarditis in her case.

In Case 178, a woman who died at the age of 78, had edema of the legs thirty years before her death, suffered from anginal attacks and paroxysms of dyspnea for eight years, had a very moderate hypertension, 170 systolic and 110 diastolic, and extensive arteriosclerosis, and finally died of lobar pneumonia.

Somewhat similar are Cases 81, 135 and 212, in men in whom the primary disease was clearly senile arteriosclerosis. In contrast to them was Case 44, in which the patient, a man dying at 46 of uremia, had his first headaches twelve years before death. He suffered from headaches, loss of flesh, transient hemiplegic attacks, dyspnea and polyuria. His blood-pressure was 255 systolic and 170 diastolic two years before death, and he died of chronic uremia. His brother (Case 41, not shown in Table 16) had an almost identical course of eight years, dying at the age

TABLE 16.—Protocol of Thirty-Seven Deceased Patients Living Ten Years and Over from Onset of First Symptom

Males

Case No.	Symptoms		Age at Death	Duration Years	Death
	First Symptom	Prominent Early Symptoms			
4	Polyuria.	Anginoid pain, polyuria, visual disturbance, loss of flesh.	70	11	Uremia.
14	Diabetes.	Gastro-intestinal hemorrhage.	63	15	Cardiac insufficiency.
17	Accidental discovery, albumin and casts.	None.	53	19	Cardiac insufficiency.
19	Anginoid pain.	Anginoid pain.	58	11	Angina pectoris.
26	Palpitation.	Paroxysmal dyspnea, albumin and casts.	52	13	Unknown.
44	Headache, typical.	Headache, typical, loss of flesh, hemiplegic attack, vertigo, polyuria.	46	12	Uremia.
48	Dyspnea on exertion.	Retention of urine.	70	16	Unknown.
67	Anginoid pain.	Anginoid pain, dyspnea on exertion, paroxysmal dyspnea, edema of legs.	58	13	Cardiac insufficiency.
81	Fatigue.	Dyspnea on exertion, slight.	72	10	Apoplexy .
86	Accidental discovery, albumin and casts.	Anginoid pain +.	52	22	Angina pectoris.
97	Renal colic.	Mental fatigue, headache typical, palpitation, neuralgic pain.	54	16	Sudden.
109	Polyuria.	None.	74	13	Pneumonia
121	Palpitation.	Paroxysmal tachycardia.	62	32	Auto accident.
129	Albumin, casts, etc.	Albumin, casts, legs giving out, vertigo, loss of flesh.	61	12	Apoplexy.
135	Oliguria.	Dyspnea on exertion, slight.	80	15	Cardiac insufficiency.
164	Neuralgic pains.	Diabetes.	63	10	Pneumonia.
165	Diabetes.	Anginoid pain.	60	10	Angina pectoris.
172	Accidental discovery, albumin and casts.	Neuralgic pains, albumin and casts.	40	13	Cardiac insufficiency.
175	Diabetes.	Diabetes, dyspnea on exertion.	73	29	Pneumonia.
176	Palpitation.	Palpitation, vertigo, dyspnea on exertion, slight.	59	16	Cardiac insufficiency.
182	Diabetes, edema of nephritic type, Anginoid pain.	Anginoid pain.	62	14	Cardiac insufficiency.
183	Albumin and casts, paroxysmal dyspnea.	Albumin and casts, paroxysmal dyspnea, hemoptysis, dyspnea on exertion, loss of flesh, cough.	65	14	Cardiac insufficiency.

TABLE 16.—CONTINUED
(MALES)

Case No.	Symptoms		Age at Death	Duration Years	Death
	First Symptom	Prominent Early Symptoms			
197	Paroxysmal dyspnea.	Paroxysmal dyspnea, dyspnea on exertion, polyuria.	68	10	Cardiac insufficiency.
211	Mild arteriosclerosis.	Cough, vertigo, headache typical, hemiplegic attack.	67	17	Drowned.
212	Palpitation.	Palpitation, dyspnea on exertion.	72	13	Apoplexy.
213	Diabetes.	Edema of legs, anginoid pain.	59	11	Pneumonia.
217	Edema of legs.	Paroxysmal tachycardia, pericardial effusion.	59	10	Pericardial effusion.
		Females			
25	Albumin and casts (pregnancy).	Loss of flesh, fatigue.	47	23	Uremia.
53	Diabetes, renal colic.	Loss of flesh, albumin and casts.	61	13	Unknown.
63	Diabetes, albumin and casts.	Neuralgic pains, albumin and casts, dyspnea on exertion, paroxysmal dyspnea, visual disturbance.	62	10	Uremia.
65	Dyspnea on exertion.	Dyspnea on exertion, polyuria, edema of lungs, palpitation.	56	10	Cardiac insufficiency.
75	Hematuria.	Hematuria, oliguria, headache typical, gastro-intestinal hemorrhage marked, gangrene of extremity, anemia.	19	10	Progressive anemia.
96	Marked gastro-intestinal disturbance, drowsiness.	Polyuria, albumin and casts.	44	13	Uremia.
103	Edema of legs.	Dyspnea on exertion, paroxysmal dyspnea.	64	15	Apoplexy.
148	Goiter.	Goiter.	55	16	Cardiac insufficiency.
178	Edema of legs.	Anginoid pain, paroxysmal dyspnea.	78	30	Pneumonia.
187	True psychosis.	True psychosis, albumin and casts, general edema, uremia.	60	11	Apoplexy.

of 37, also of chronic uremia. In these two men, headache of the kind I have described, of the most intense character, was wholly unrelieved by any methods of treatment.

Cases 19 and 67 are noteworthy as illustrating the occasional long tolerance of anginoid pain. In each of these men, this was the first and throughout the prominent symptom, yet the former lived eleven years, dying finally of an anginal seizure, and the latter succumbed to gradual cardiac insufficiency only after thirteen years.

A. Duration of Illness in Relation to Causes of Death.—The duration of illness from the first symptom to death is shown arranged by causes of death in Table 17.

TABLE 17.—THE RELATION OF DURATION OF ILLNESS (FIRST SYMPTOM TO DEATH) TO CAUSES OF DEATH

Causes of Death,	Duration (years)									Total	Median Year
	—1	1	2	3	4	5	6*	Per-centages	Unknown		
Cardiac insufficiency	9	3	10	5	5	4	19	34.5	5	60	4
Uremia	3	8	6	10	4	4	11	23.9	0	46	3
Apoplexy	2	1	4	4	4	6	7	25.0	1	29	4
Angina pectoris	0	1	0	2	3	1	3	30.0	0	10	4
Edema of the lungs	0	0	3	1	1	2	0	0.0	0	7	3
Acute infectious disease	2	1	0	2	1	0	6	50.0	1	13	5
Progressive anemia	0	0	0	1	0	0	2	66.6	0	3	..
Pericarditis	0	0	0	0	0	0	1	100.0	0	1	..
Accidental causes	0	1	1	2	1	1	3	33.3	0	9	..
Sudden	0	1	1	0	2	1	1	16.6	0	6	4
										186	

* And over.

NOTE.—The percentages of the column, 6 years and over, have been compiled on the basis of the cases in which the death was known, eliminating the unknown.

The differences here are not very great between the groups. But, judged either by the median for duration or the number of patients living six years and over, the group dying with uremic symptoms seems to be somewhat shorter-lived; 75 per cent. of these patients died before the sixth year. There were too few persons dying of edema of the lungs to make it safe to draw any conclusions, but it is interesting that the whole seven died before the sixth year of illness. The distinctly greater duration in the case of patients dying of acute infectious diseases is of still more significance when one considers that such intercurrent infection must be looked on as an accident terminating the underlying chronic disease before it would in itself have led to a fatal issue. It seems fair to conclude, then, that these patients exhibited a less progressive type of cardiovascular disease than the others. I think it is also of some interest to observe that the duration of life in patients dying of angina pectoris

was not materially different from patients dying of gradual cardiac insufficiency; in each case, at least 30 per cent. lived for six years and over from the onset of the first symptom.

In the case of the patients living June, 1912, Tables 18, 19 and 20, of first and early symptoms, show their general character.

TABLE 18.—EARLY SYMPTOMS OF 51 PATIENTS (28 MALES AND 23 FEMALES) LIVING JUNE 1, 1912, MORE THAN TEN YEARS FROM ONSET OF FIRST SYMPTOM

Symptoms	Total No. of Patients	As a First Symptom in
Dyspnea (on exertion and paroxysmal)	20	6
Anginoid pain	16	6
Edema of lungs	2	0
Palpitation	13	8
Edema of the legs	8	1
General edema	1	1
Polyuria	6	2
Retention of urine	2	2
Headache*	12	1
Vertigo	9	3
Hemiplegic attacks	5	1
Transient coma	1	1
Uremic convulsion	1	0
Drowsiness	1	0
Visual disturbances	1	0
Pains (mainly neuralgia)	8	3
Fatigue (physical and mental)	6	1
Hemorrhages	3	0
Loss of flesh	2	0
Gangrene of extremities	1	1
Intermittent claudication	4	1
Cough	1	0
Diabetes	10	6
Albumin and casts (accidental discovery)	3	3
Cardiac disturbance (accidental discovery)	2	2
High blood-pressure (accidental discovery)	1	1

* Of these cases of headache, three were typical, nine atypical; the case in which headache was the first symptom was of the atypical type.

TABLE 19.—AGES OF FIFTY-ONE LIVING PATIENTS (28 MALES AND 23 FEMALES) WITH SYMPTOMS MORE THAN TEN YEARS FROM ONSET

From 30 to 39 years	3	From 70 to 79 years	9
From 40 to 49 years	4	Eighty and over	3
From 50 to 59 years	15		
From 60 to 69 years	17	Total	51

TABLE 20.—DURATION OF ILLNESS, FIRST SYMPTOM TO JUNE 1, 1912, OF FIFTY-ONE PATIENTS LIVING FOR TEN YEARS AND LONGER FROM ONSET OF FIRST SYMPTOM

Years	Number	Years	Number
10	12	14	0
11	6	15	5
12	9	Over 15	14
13	5		51

It is evident that in a considerable number of instances, the first symptom was one of a minor nature — palpitation, vertigo, or pains, or a preceding disease, such as diabetes. There were, however, six patients who had dyspnea, six who had anginoid pain, one who had edema of the legs, one with general anasarca, one a hemiplegic attack, and one an attack of coma more than ten years ago who were still living in June, 1912. In six the discovery of their condition was purely accidental. The most significant point in the tabulation of these blood-pressures (Table 21) is that the median for this group of long duration is exactly the median for the entire living group, that is, 200 mm. This, again,

TABLE 21.—Blood-Pressures of Fifty-One Patients Living More Than Ten Years from Onset of First Symptom

Blood-Pressure, mm.	No. of Patients	Blood-Pressure, mm.	No. of Patients
165-170	4	235-240	3
175-180	5	245-250	3
185-190	10	255-260	1
195-200	6*	265-270	2
205-210	8	275-280	1
215-220	7		—
225-230	1	Total	51

*Median.

TABLE 22.—Duration of Life After Finding High Blood-Pressure, 438 Patients

Dying in	Deceased (to Death)				Living (to June, 1912)			
	Males		Females		Males		Females	
	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
Less than one year...	73	49.0	27	55.1	51	37.0	38	37.3
One year and over...	32	21.5	10	20.4	13	9.4	12	11.8
Two years and over..	14	9.4	2	4.1	13	9.4	10	9.8
Three years and over.	12	8.0	4	8.2	18	13.1	8	7.8
Four years and over..	10	6.7	4	8.2	19	13.8	12	11.8
Five years and over..	4	2.7	1	2.0	10	7.2	9	8.8
Six years and over...	4	2.7	1	2.0	14	10.1	13	12.7
Total	149	100.0	49	100.0	138	100.0	102	100.0

indicates that the exact height of the blood-pressure has very little prognostic value. Of course, it must be remembered that these blood-pressure readings are not in all cases the pressures of ten years ago. The study of these patients suggests the need for extreme reserve in making any prognosis as to the probable duration of life in this type of chronic disease.

2. The Duration of Life after Finding High Blood-Pressure.—The duration of life after my discovery of high blood-pressure in the deceased patients and in those still living is shown in Table 22.

Since my accurate readings date back but ten years, these figures are useful only as suggesting future possibilities. All but 2.7 per cent. of the men and 2 per cent. of the women died within five years of my discovery of hypertension. The few living from six to ten years later, however, show that the duration of hypertensive cardiovascular disease may easily exceed ten years. Absolute information on this point will eventually be afforded by the large life-insurance companies. An excellent start has been made in this direction by such work as that of Fisher.[15]

X. ETIOLOGY

When this work was undertaken I had hoped that it might also be possible to correlate information of value as to possible etiological factors contributing to the development of arterial hypertension. The range of such factors as were found in the life histories of these persons was so great as to demand an extensive critical study to yield anything more than the usual text-book catalogue of all the diseases and vices of the human race as the causes of any disease the origin of which is obscure. This attempt was, therefore, for the time being abandoned, in order to devote more attention to the foregoing facts bearing on the clinical features and the prognoses of the morbid state, which, while less important than a knowledge of its cause, seems also less likely to mislead. A similar discussion of the etiology seemed likely to provoke the criticism made by Artemus Ward that "it is better not to know so many things than to know so many things that ain't so."

XI. GENERAL CONSIDERATIONS

The question may well be asked whether there is any warrant for bringing together, as I have done, cases of so diverse a nature, which had in common only the single symptom, high blood-pressure. Throughout the preceding pages, I have purposely refrained from indicating the clinical diagnoses in these cases. I have done this because the clinical diagnoses which I made ten years ago are not the clinical diagnoses which I would make in the same patients to-day, and I trust that they are not the diagnoses under which such cases will be tabulated ten or twenty years hence. I have endeavored to limit myself to a statement of facts and obvious numerical relationships. Neither the clinical studies of nearly a century, nor the experimental investigations of nearly half a century have succeeded in elucidating the real cause of high blood-pressure, nor have the anatomical researches of pathologists resulted in any unanimity of opinion about the relationship of the underlying lesions to one another and to the disease picture. One physician would make the

15. Fisher: The Diagnostic Value of the Use of the Sphygmomanometer in Examinations for Life-Insurance, Meeting of Association of Life Insurance Medical Directors, Oct. 4, 1911, New York.

diagnosis of chronic interstitial nephritis in the bulk of these patients, another of arteriosclerosis, a third would take the purely symptomatic point of view and speak of many of them as cases of arterial hypertension. But the latter cannot be a finally satisfactory concept. The adrenalinemia theory, which has had so much vogue of late, is, as I have endeavored to show elsewhere,[16] without foundation as yet. It is evident that a large proportion of these patients show at necropsy one or another type of kidney disease, most commonly either the so-called primary contracted kidney, or arteriosclerotic atrophy. In some, however — and I have recently had brilliant examples of this — the kidney lesions are of the most insignificant character, but wide-spread arteriolar disease exists elsewhere. The tendency is strong for pathologists to return to the original view of Gull and Sutton[17] that this type of disease is primarily a disease of the small blood-vessels.

The character of the lesions has been well described by Jores.[18] The question remains open, however, whether the high blood-pressure precedes or causes the lesion. That the arterial narrowing will heighten a pre-existing high blood-pressure and render it more permanent does not make it clear that the arterial lesion comes first. That arteriosclerosis of the larger arteries may at times extend toward the periphery and produce a similar type of disease is also clear. Beyond that, it seems probable that the high blood-pressure seen as a symptom in the more acute inflammatory affections of the kidney must be dependent on other causes than this particular arteriolar disease.

The foregoing study seems to me to show clearly, if it shows anything, that the symptom pictures presented may consist of almost any set of combinations in any of these types of disease, and that clinically a satisfactory anatomical diagnosis is almost impossible. Further study by tests of renal function may help in differentiation, but for the present the physician who goes to the necropsy table expecting to be right as to the gross or minute anatomical lesions in these patients with high blood-pressure will frequently meet disappointment. For this reason — because it emphasizes both the existence of real anatomical lesions and the relation to them of the unifying physiological disturbance — I prefer for the present to speak of all these patients as cases of hypertensive cardiovascular disease. When this condition becomes engrafted on an obvious primary inflammatory nephritis, I consider it secondary hypertensive cardiovascular disease. When it originates insidiously and the urinary

16. Janeway, Theodore C.: Nephritic Hypertension: Clinical and Experimental Studies, Am. Jour. Med. Sc., 1913, cxlv, 625.

17. Gull and Sutton: The Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney, Med.-Chi. Tr., 1872, lv, 273.

18. Jores: Kritisches zur Lehre von der Nephritis and den Nephropathien, Med. Klin., 1913, ix, 18.

changes are part and parcel of the picture from the start, or follow later, I consider it primary hypertensive cardiovascular disease. The results of these processes entail danger from the point of view of the heart, the arteries, especially the cerebral arteries, or of eventual kidney atrophy below the factor of safety for the human kidney.

XII. CONCLUSIONS

1. The most prominent symptoms associated with high blood-pressure are circulatory rather than renal. The disease underlying high arterial pressure is predominantly a disease of the circulatory system, and is best designated hypertensive cardiovascular disease, either primary, or secondary when preceded by an inflammatory nephritis.

2. Death in this type of cardiovascular disease, among patients in private practice, occurs in the following ways, arranged in the order of their frequency: First, by gradual cardiac insufficiency; second, with uremic symptoms; third, by apoplexy; fourth, from some complicating acute infection; fifth, in an attack of angina pectoris; sixth, from purely acidental and unrelated causes; seventh, in a paroxysm of acute edema of the lungs; eighth, after the manner of cachexia.

3. The early symptoms associated with hypertensive cardiovascular disease have an important prognostic significance which can be utilized therapeutically, particularly for the institution of safeguarding treatment.

4. The early occurrence of symptoms of myocardial weakness, especially dyspnea, indicates a more than 50 per cent. probability of an eventual death by cardiac insufficiency. In these patients, to safeguard the heart is the main therapeutic indication.

5. The early occurrence of anginoid pain on exertion does not indicate a probability of death in an anginal paroxysm for more than one-third of the patients. It does indicate a probable cardiac death of some type. The therapeutic indications here are similar to the foregoing, except as modified by the existence of syphilitic aortitis. Anginal attacks as compared with other cardiac symptoms do not materially affect the expectancy of life.

6. Polyuria, particularly if nocturnal, indicates the probability of a uremic death for more than 50 per cent. of the patients. It is not essential to safeguard the heart in these patients, unless associated cardiac symptoms exist.

7. Headache, especially that heretofore described as typical, indicates the probability of a uremic death for more than 50 per cent. of the patients, and of the death from apoplexy for a considerable number of the remainder. The therapeutic indications are similar to those of polyuria.

8. Loss of flesh, if marked and progressive, is a symptom of bad prognostic import.

9. The relation of the height of the blood-pressure to prognosis is doubtful. Systolic pressures persistently well above 200 mm. Hg seem to indicate a greater probability of death by uremia or apoplexy. The exact height of the blood-pressure does not seem to have much bearing on the expectancy of life.

10. The average duration of life in this group of patients, after the onset of symptoms associated with high blood-pressure, has been four years for the men and five for the women. One-half of the whole number of deceased died during the first five years. One-quarter of the number lived between five and ten years, and the remaining quarter over ten years from the appearance of the first symptom. The existence of this considerable number of patients living for a long period of time suggests the need of great caution in making a prognosis as to expectancy of life.

I wish to express my indebtedness to my secretary, Miss Anna L. von der Osten, for the large amount of statistical work extending over a year and a half represented by these studies; and to acknowledge with thanks the occasional helpful suggestions on statistical problems afforded by Dr. Leonard P. Ayres of the Russell Sage Foundation.

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BOOK REVIEWS

STAMMERING AND COGNATE DEFECTS OF SPEECH. By C. S. Bluemel. Cloth. Price, $5 net. Two Volumes. Total pp. 756. New York: G. E. Stechert & Co., 1913.

This book treats the subject in a most original manner. The author leads up logically to his conclusions by discussing in the first chapters of the first volume many psychological facts, and especially those which pertain to speech. Different aspects of their bearing on the different phases and peculiarities of stammering are taken up. After an exhaustive consideration of the psychological conditions which are present in stammering Bluemel comes to the conclusion that "the primary cause of stammering is auditory amnesia. The secondary or auxiliary causes are bewilderment, perversion of the verbal image, autosuggestion giving rise to inhibition of the will and finally to fear."

The efforts of most systems leading to the correction of stammering have been directed toward these secondary or auxiliary causes and have been successful only inasmuch as these causes overrule the picture. For instance, the elocutionary systems will usually overcome the physical errors such as respiration, articulation, etc. They are good as far as they go, but they do not go far enough. The time beating system is, according to Bluemel, directly pernicious since it distorts the stammerer's verbal imagery. He believes that the stammerer should be encouraged to commence articulation because in this way he stimulates the action of the auditory speech center. This may be done in other ways, as, for instance, by associating certain vowel sounds with colors, or when a vowel is to be pronounced appealing to the visual rather than to the auditory sensation. He believes that the attention of the stammerer should be centered on the refractory word. He states that "if a complete and permanent cure is to be effected the stammerer must cease to depend on auditory images, for so long as he relies on these speech cues he must inevitably stammer when amnesia occurs."

In these many ways he points out the direction toward which treatment of stammering should go.

The second volume takes up the various systems now in vogue for the treatment of stammering and discusses their bearing on the subject of auditory amnesia.

These two volumes constitute a most original presentation of the subject, and certainly bear the stamp of deep and independent thought. Whether one agrees with the ideas expressed or not, he must feel that the work is a valuable contribution on the subject.

STUDIES CONCERNING GLYCOSURIA AND DIABETES. By Frederick M. Allen, A.B., M.D. Cloth. Price, $9. Pp. 1179. Boston: W. M. Leonard, 1913.

The avowed purpose of this work is an application of such knowledge as can be gained by experiments on animals to the evolution of an improved therapy for diabetes in man. Its preparation has occupied the author three years and these must indeed have been years of most arduous toil and industry for, in bulk alone, the volume before us far exceeds anything that has ever been written in the difficult and confusing field of glycosuria and diabetes. The knowledge that so large a volume has occupied so short a time in its compilation, would ordinarily lead us to expect a considerable amount of slip-shod and undigested matter, but this is by no means the case; from cover to cover the pages of the book are filled with material that is directly or indirectly applicable in such a detailed study as the work professes to be.

In general, the book consists of a literary review of previous work and of a detailed account of the author's own experiments. Since such an account has not previously been published much space is occupied in doing so, and this in part accounts for the large size of the volume.

In the first five chapters the general effects of excessive sugar assimilation are discussed. After briefly reviewing the development of knowledge regarding the nature and amount of sugar in the blood and urine the author proceeds to show how contradictory and confusing are our present-day views regarding the assimilation limits of the various sugars. He points out to what degree differences in species and in the physiological state of the animal, as well as differences in the chemical nature and method of administration of the sugar have been found to influence the results. He states that "if it is desired to rule out every possible irregularity of absorption and to test the simple saturation limit the intravenous method may be useful" whereas, "for a test of the rate at which the tissues utilize sugar the subcutaneous is the method of choice."

As an outcome of this review and supported by experiments of his own, the author concludes that a fundamental distinction exists in the power with which the organism uses sugar in normal as compared with diabetic animals. It is only in the diabetic organism that any real limit of assimilation exists, the traces of sugar which may escape in the urine of normal animals being more or less accidental and in no way indicating that an assimilation limit has been reached. This behavior of dextrose in normal animals is designated as dextrose paradox.

The disappearance of this "paradox" is the most reliable test for the existence of the diabetic state in that "it furnishes a demonstrable and absolute theoretical distinction between diabetes and every other form of glycosuria." It is pointed out, however, that it is probably only in laboratory experiments that the test is of value; in clinical practice, most cases of diabetes retain so extensive a sugar burning power that the paradox is still evident.

Several other facts of practical importance concerning the effects of excessive sugar ingestion are considered. It was found, for example, that repeated sugar injections in cats did not lower the tolerance nor did they necessarily lead to fat deposition; in fasting animals they assist the general strength and well-being, "they furnish spending money, not reserve capital;" they may therefore be useful in weakened conditions. After confirming these observations by experiments on puppies a valuable résumé is given, at the end of Chapter V, of the therapeutic use of dextrose injections.

Perhaps the most original contribution in the book concerns the effects which are produced on the excretion of urine by injections of sugar in normal as compared with diabetic animals. In normal animals of various species all the freely utilizable sugars cause anuria when given otherwise than intravenously, but by this method they all cause diuresis. In diabetic animals on the other hand, dextrose causes diuresis in whatever way it is given. Most of the fallacies which might be thought of as entering into the experiments from which these conclusions are drawn are critically considered and the criticisms appear to be adequately met. It is unfortunate, however, that more care was not taken in making certain that the bladder was emptied at the end of each observation period. The anuria and subsequent polyuria following subcutaneous injections of such irritant solutions as 80 per cent. dextrose may have been due solely to reflex bladder retention. The amboceptor hypothesis which is invoked to explain these results is at least ingenious. By subjecting the various forms of experimental glycosuria to the above diuresis-test it was found that none is truly a diabetes except that supervening on complete depancreatization.

Most interesting and well-arranged reviews are given on such subjects as the classification of the various forms of glycosuria, on adrenalin, phloridzin and the nervous system of glycosuria, on the anatomical changes in the pancreas, on therapy, etc. The chapter on the polyglandular doctrine is the best that we have read on this modern-day phantasy.

As a well written review of a great part of the enormous literature that has accumulated in the domain of experimental diabetes and as a most suggestive thesis, the book is to be highly commended. The reviews of the work of previous investigators are clearly and accurately stated and they are well arranged in relationship to one another. A most valuable bibliography completes the volume.

IRRITABILITY. By Max Verworn, M.D., Ph.D., Prof. at Bonn Physiological Institute. Memorial Lectures under the Stilliman Foundations at Yale University. Yale University Press.

No single condition in a process in the least complex can be considered causal; rather the evolution of a process depends on all conditions being in proper order. All changes in vital conditions act as stimuli. In the present work, however, only changes in the external world are considered as stimuli; changes within the organism are considered as development.

Stimuli are considered as to their amount, quality (negative or positive), intensity, form and rapidity. Under intensity Fechner's law (the intensity of sensation varies with the logarythm of the intensity of the stimulus), and the "all or none law" (any response is the most complete response possible, i. e., the heart beat) are discussed. Stimulation also causes a qualitative change in vital processes metabolically, a practical differentiation from the constant change going on in the metabolism of rest or equilibrium of metabolism. In equilibrium of metabolism $\frac{\text{assimilation}}{\text{dissimilation}} = 1$, i. e., biotonus. Stimuli are likened to catalyzers: not appearing in the resultant state. They act on the "specific energy" of vital processes (eyes give only visual sensation, organs of taste only gustatory), either increasing (exciting) or decreasing (depressing) their activity. Stimuli also act to alter processes qualitatively, directing chemical changes into new channels. Examples of this are the changes occurring under constantly recurring weak stimuli as in chronic disease or constant ingestion of alcohol. Disease is life under altered conditions, and altered vital conditions are stimuli: disease brings about new conditions.

Metabolic processes must be considered as being morphologically associated in a branching arrangement somewhat after the formation of Ehrlich's side-chain diagrams with relatively stabile and labile elements. The end products of the labile elements, waste products, may act as stimuli (altered vital conditions) and cause a secondary reaction such as fatigue. Rest and restoration then come about as evidence of a self-regulatory metabolic mechanism. Development is one aspect of the constancy of metabolic activity; death is another. In the latter the stimulation of waste products is greater than metabolic restoration.

To understand the result of stimulations one must understand the latent period and the production of energy. The latent period is occupied by changes rising from zero to a point appreciable by our indicators. With the fewest possible exceptions these are at first dissimilative or breaking down changes. They affect the functional, N-free, labile elements of metabolism, and result in the easily diffusible end-products, H_2O and CO_2. Weak acids cause increased blood supply. Therefore functional hypertrophy, with increased formation of the eliminative substances, among them carbonic acid, results in increased blood supply. Increased blood supply leads to increased oxidation, more energy, and true hypertrophy. The conduction of stimuli in pseudopodia of difflugia, poorly conducting protoplasm, is influenced by intensity and distance. Apparently this is not so in medulated nerves where the all or none law rules.

As a vital process occurs (the contraction of a muscle) oxidizable substances are broken down. The destruction of these substances as well as the presence of the resultant waste products reduces irritability. These labile substances, and with them irritability, are restored by metabolic self-regulation. Where the all or none law does not hold, disintegration is not complete, sufficient stimulus can cause a reaction, and the refractory period is relative. Where the all or none law rules, there is disintegration of all labile substances, irritability is at zero, and

the refractory period is absolute. Fatigue is asphyxiation; is the refractory period prolonged by a relative lack of oxygen.

The response to repeated stimuli depends on the irritability of the system at the moment of repetition. Oxidizable substances are being both broken down and built up during the refractory period. If the former is in the ascendance, irritability is diminishing, if the latter, increasing. The first result of each stimulus is a breaking down and therefore if the stimuli are repeated rapidly enough response is inhibited. If a sufficient interval intervenes the responses may be repeated, or even in heterobolic tissues (where the all or none law does not rule) may be summated.

Depression or retardation of vital processes can be most frequently explained on a basis of diminished oxidization. A depressant like a narcotic, for instance, diminishes oxidization and interferes with energy production. If O is transmitted to oxidizable substances by a carrier acting as a catalyzer the assumption that narcotics interfere with the carrier agrees with all the known facts concerning the action of narcotics. Other depressants (cold, fatigue, etc.,) likewise act through their interference with the processes of oxidation.

All the conclusions drawn in this work are well illustrated by numerous examples.

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